

THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

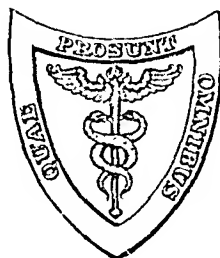
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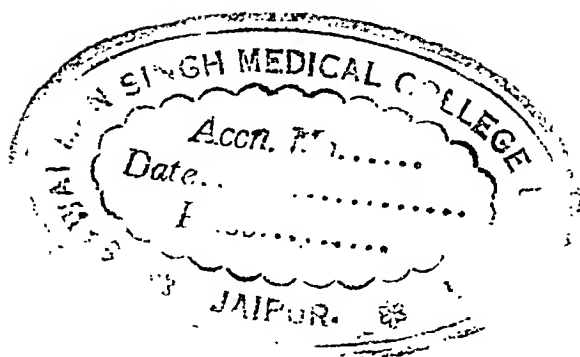
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THE
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ORIGINAL ARTICLES.

ALTERATIONS IN THE VOLUME OF THE NORMAL SPLEEN AND
THEIR SIGNIFICANCE.

BEING THE TWENTY-FIRST MARY SCOTT NEWBOLD LECTURE OF THE
COLLEGE OF PHYSICIANS OF PHILADELPHIA.

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THE work of three men whose names appear on the roll of this College, Pearce, Krumbhaar and Frazier,¹ has to me been so great a source of inspiration as to make this evening one which will always stand out in my memory. The pleasure, of discussing the change of volume of the spleen in Philadelphia is as great as the sense of honor which I feel in being asked to do so by a society which numbers among its members some of those whose opinions on this subject are of outstanding authority. My own methods are perhaps different from most used by them and my only regret is that the occasion is that of a lecture rather than a medical exchange of experience.

Let me commence by stating very shortly, and so disposing of, certain inevitable methods of technique.

The object has been to form some estimate of the alterations in volume of this spleen when the animal is in full health and exercising his normal functions. Anesthetics must be barred and even the plethysmographic methods, so fruitful in the hands of Hargis and Mann,² and of Heymans,³ have not been used because they postu-

late quiescence on the part of the animal. I have had recourse to two principal methods of investigation:

1. That of performing a preliminary operation in which small metal clips were placed along the edge of the spleen, and when the effects of the operation had entirely worn off, judging of the size of the organ by means of Roentgen ray photographs taken in the horizontal and vertical planes; from which photographs a presentable reconstruction can be made of the lineal outline (Barcroft⁴ and others).

2. An operation by which the spleen, without injury to its vascular and nervous attachments can be withdrawn through the body wall and fixed in a position outside of the skin. In this position the organ rapidly makes itself at home, so much so that it ultimately becomes covered by a delicate epithelium like that of the lip and is then proof against any but gross injury (Barcroft and Stevens⁵).

By either of these methods large alterations in the volume of the organ may be seen rapidly to take place. So large indeed are they as to convince the observer that the spleen may on occasion contain perhaps one-fifth of the whole blood volume.

The principal experimental procedures which will lead to the rapid disgorgement of this blood are, asphyxia, carbon monoxid poisoning, exercise, hemorrhage, and as has been shown by Hargis and Mann,² and by Cannon and Izquierdo,⁶ emotion.

I pass over these acute effects very briefly because they have already been described in print and I pass to certain effects which extend over longer periods of time, concerning which less has been already published. One comment, however, I must first make in the cases of hemorrhage and of exercise: the contraction of the spleen, is not as I had once supposed, a final effort on the part of the body to add to the blood volume. It is a very early effect, a kind of fine adjustment; like all fine adjustments, though useful, is not indispensable.

Prolonged Contraction of the Spleen. *The Effect of Pregnancy.*⁷ The first experiments in which the spleen was exteriorized were, of course, somewhat of a speculation. These were carried out in the early summer of 1926. When the phenomenon of the contraction of the spleen on exercise had been fully established it became our intention to take one, at least, of the three animals in our possession to show at the Physiological Congress at Stockholm. The question was which should it be? We placed the dogs in an order of merit and the order remained undisturbed until a few days before the date of departure for the Congress. Then the spleen of our best animal suddenly became small and pale. The animal itself became extremely disinclined to take exercise and when it did so the contraction of the already small spleen was not very well marked. We were, of course, greatly disappointed, partly because our best specimen had failed and partly because the possibility was introduced that the exercise contraction of the spleen was a less constant phe-

nomenon than we had supposed. However, two quite good specimens remained. These were taken to Stockholm where the best alas was run over in the street by a motor bus. The remaining animal, however, proved quite a convincing demonstration of exercise contraction.

To return to the animal which we decided not to take. It was killed just before we started; our laboratory assistant Sergt.-Major Secker, R. A. M. C., performed a postmortem upon it and on our return from Stockholm we were greeted with the information that the uterus of the animal had contained fetuses in a fairly advanced stage of development. It must be confessed that we did not at once grasp the significance of what had taken place.

A second "accident," however, focussed our attention on the subject. We exteriorized the spleens of two dogs. Both spleens ran a somewhat similar course for a while, then one suddenly became much smaller and pale. It had shrunk in a few days to half its surface. Then one morning we came into the laboratory to find 7 puppies. From this time the spleen gradually enlarged. Ultimately partly because of the continued gradual shrinking of the spleen of the control animal and partly because of the gradual enlargement of the spleen of the recently pregnant one, the two became almost the same size.

From this time we undertook some systematic observations in the subject of the relation of pregnancy to spleen volume.

The technique at first was similar to that which has just been described. A bitch was "covered" by a dog: at the same time another of about the same size was chosen as a control. Four to five weeks afterward the spleens of the two were exteriorized. As the period of gestation in the bitch is sixty-three days, there remained about four weeks and a half in which the spleen could settle down. Usually it is not possible to make any comparisons which are of value for the first ten days. The size of the spleen depends upon the operative procedure for that period—a little more or less pressure on one of the splenic vessels will make a considerable difference. After that, about ten days, the comparisons between the "probably" pregnant and the control bitches were instituted. In each case there was little to choose in size between the spleens of the two animals at that stage, but in the last fortnight or ten days' pregnancy, the spleen of the prospective mother shrank to an insignificant size and became very pale, enlarging again after the birth of the pups and ultimately attaining the size of that of the control animal. Once the spleen had attained the same size they ran a pretty equal course, both gradually shrinking for a time. The least satisfactory feature of these experiments was that we were comparing the variations in the size of the spleen of the pregnant bitch not with a control whose size remained the constant or practically constant, but with one which itself was gradually shrinking. At that time we had not

discovered that after the spleen has been exteriorized for several months the volume changes relatively little. That discovery was made on an animal which had been used as a control in one of the above experiments. After her spleen had settled to a volume of relative constance it happened that she came on "heat." She took the dog successfully and so we had the opportunity of investigating the effect of pregnancy on a bitch whose spleen, apart from the demands of her reproductive organs would have remained of relatively constant volume over a period of nine weeks.

The spleen showed a marked but passing contraction during the period of "heat." This was only a matter of a few days. It returned to its former size and no material alteration took place until nearly half way through the pregnancy. The spleen then commenced to shrink and reached its minimum size about four days before the birth of the pups. During those four days it altered but little, growing if anything, but directly after the pups were born the spleen rapidly became more turgid and within twenty days it was larger than at any time during the previous six months. Such is a rough outline of the facts. There are one or two points to be cleared up before we discuss their interpretation.

There is usually a certain amount of anemia associated with the exteriorization of the spleen. Could it be that the alleged pregnancy shrinkage was really a result of anemia, not in truth a primary result of pregnancy. Hemoglobin determinations were made throughout the course of the experiment last quoted. The hemoglobin percentages were as follows:

Three months before pregnancy	Hb = 80.0
During heat	Hb = 74.6
During first half of pregnancy	Hb = 75.6
During second half of pregnancy	Hb = 70.2
During twenty days after	Hb = 72.2

The above results show that during the period of "heat" when the spleen was contracted, the hemoglobin values were not sensibly lower than they had been previously. Throughout the whole of the pregnancy they remained in the vicinity of 70 with one or two exceptions, at which level they were at the time of birth and for some time subsequently. Moreover the research of Shen⁸ showed that, while bleeding caused a shrinking of the spleen, the fact of a low hemoglobin value did not necessarily do so.

Postoperative Contraction of the Spleen. During the course of experiments in which parts of the intestine were exteriorized,⁹ some time after exteriorization of the spleen, some quite unexpected observations were made.

In the first two experiments of the series a loop of small intestine was withdrawn and placed outside the abdominal wall.¹⁰ In both cases the animal seemed to do well even though the gut had not been severed and the food had to pass along the exteriorized portion.

Neither dog, however, lived very long, the ultimate trouble in each case being perforation. In one animal the lesion was in the abdominal cavity. The dog suddenly became ill; the condition clearly being hopeless, it was killed. The postmortem examination showed a general infection of the abdomen.

The perforation in the other animal took place in the exteriorized portion; it was due to an accidental cause, namely, that the dog swallowed a piece of bone about 4 inches long. This was unable to get round an angle where the gut was fixed to the abdominal wall. In both these cases the spleen became quite small during the operation and did not regain the size thereafter. Indeed in the first case, that in which general peritonitis developed, the spleen shrunk even more than it had done; it was at its smallest when the animal died.

The question arose: Had these animals survived, would their spleens ever have attained to a size as great as that which they would have occupied if the subsequent abdominal operation had never been performed?

One experiment has taken place in which a portion of gut has been exteriorized with perfect success by Florey,¹¹ after the spleen had been exteriorized some two months previously. There was no indication of any general or even local infection. Nevertheless, the spleen again shrank to about half the previous size and remained so for about four weeks. After that time it dilated and attained the size which judging from a control dog, it would have occupied if no intestinal operation had taken place. Here again we are in the dark as to whether the contraction was due to a nervous reflex or to some substance absorbed from the wound or elsewhere.

Significance of the Splenic Contraction. Having studied some of the phenomena, for their own sake, which the contraction of the spleen presents, we may now turn to the consideration of the question of what significance may be the splenic contraction. Let us go back to Gray's original thesis that the function of the spleen is to control the quantity and quality of the blood.

The Regulation of the Quantity of Blood. Three factors appear to be connected, though the precise numerical relation between them is not as yet worked out.

1. The volume of blood in the body.
2. The volume of the bed in which it circulates, that is, the pressure under which the blood would be in the body if the whole circulation ceased.
3. The volume of blood which circulates per minute round this vascular system over short periods of time.

If, for instance, a certain quantity of blood is injected into the circulation, all observers (Daly,¹² H. Barcroft¹³ and Jarisch¹⁴) agree that, other things being equal, the circulation rate will be increased.

They agree moreover that in the closed heart-lung preparation

or in the intact but brainless animal the rate of increase expressed in cubic centimeters per minute is of the order of ten times the amount of blood injected. Thus, as will be seen from the following picture, roughly 20 cc. of blood injected will produce an increased flow of 200 cc. of blood per minute round the body.

Suppose then a dog to have a bloodflow of 1 liter of blood per minute round his body and suppose that the spleen adds to that 100 cc. of blood. The increased bloodflow is found by multiplying the 100 cc. of added flow by ten, and is therefore 1 liter. The effect then has been to increase the ratio of bloodflow from 1 to 2 liters per minute.

In the case of exercise such an increase forms an appreciable proportion of the whole augmentation which takes place.

Moreover, the significance of the addition of blood from an outside source, such as the spleen, does not end with the statement which has just been made.

Among the various factors which conspire to give momentum to the blood when exercise is taken, is the augmentation of the depth of respiration.¹⁵ Now if I understand aright, the effect of deepened respiration on bloodflow is not so much to add to the velocity of the circulating blood, but to multiply it by a factor.

Let me ask a question. If a certain degree of dyspnea increased the minute volume of blood from an initial value of 1 liter to a final value of 2 liters, would the same degree of dyspnea augment an initial value of 2 liters into a final value of 4 liters? I am not prepared to make definite statement in the affirmative, nevertheless there does seem to be that element about the effect of dyspnea. It is a sort of amplifier and therefore any other factor which adds to the minute volume, has in exercise a significance beyond the face value owing to this effect of the dyspnea which follows and amplifies it.

The word "follows" if not actually used advisedly is used not quite casually. The events which lead up to exercise are often gradual and, as the result of suitable emotion contraction of the spleen, may precede the actual exercise, in which case the splenic increase of the minute volume would precede so much of the dyspnea as is caused by altered hydrogen-ion concentration of the blood.

Hemorrhage. Let us pass to the significance of hemorrhage in relation to spleen volume.

Striking as are the results produced by the injection of blood, the results produced by its withdrawal are perhaps more so. The withdrawal of 100 cc. of blood from a closed heart-lung preparation reduces the minute volume of blood from 1.5 liters per minute to 0.5 liter per minute. But so far as is known, a very early effect of hemorrhage on this intact animal is to produce contraction of the spleen

and in the cat about $\frac{1}{15}$ of all the blood may be taken from the vessels without any sensible fall in the volume of the circulating blood. Applied to a dog of 15 kilos, that would mean that 100 cc. of blood could be taken out without appreciably reducing the quantity of blood in circulation. After that 100 cc. had gone, the minute volume would commence to pay a heavy tax on every further cubic centimeter of blood withdrawn.

More Chronic Compensations. Apart from the rôle of the spleen in buffering mechanically the vascular system against sudden emergencies in the circulation such as those caused by hemorrhage, exercise, etc., there remained to be considered such questions as the rôle in pregnancy, intestinal operations, alterations in skin temperature, etc.

About these matters we know but little; a calculation made on the basis of some work by Uyeno¹⁶ suggested that the total volume of blood which coursed through the skin vessels if dilated by heat might be about 3 liters in man per minute. This is of course associated with a considerable increase in the size of the vascular bed in the skin vessels. Clearly these alterations could be effected without any alteration in the total minute volume, of the total vascular capacity by the cutting off of blood from other areas. But to supply 3 liters of blood per minute to the skin would on that basis mean the diversion of anything from 40 to 90 per cent of this whole blood-flow to the skin and have little for the essential organs of the body. It seems rational therefore that if the vascular bed is enlarged the blood volume should be enlarged in proportion, that is to say, so that the blood exerted the normal pressure in the vessels. And indeed experiments, other than the original observations on our way to Peru,¹⁷ have shown an increased bloodflow as the result of residence in a warm chamber. The provision of corpuscles to meet the increased bloodflow may be a legitimate function of the spleen; the matter could easily be tested on an animal with an extracutaneous spleen, but that has not been done.

Operations. We are still more in the dark as regards the shrinkage of the spleen in intestinal operations. Here the weak point in the argument is not whether or no the spleen contracts, but whether or no there is any commensurate increase to the vascular bed. This matter again is under investigation.

Pregnancy and Heat. The evidence with regard to these alterations is on the whole more satisfactory than with regard to either postoperative shock or exposure to warm climates, because we know that we have both a large increase in the vascular bed of the generative organs and a decrease in the size of the spleen. The point unproven here is the actual increase in the blood volume in dogs. But insofar as it is legitimate to transfer information culled from one form of life to another, these experiments seem to form a natural

complement to those of Rowntree,¹⁸ who found a rise with vital red in the blood volume much beyond the amount of the fetus—the method was that of vital red injection which in any case could not by the very nature escape from the maternal blood. The rise commenced about the middle of pregnancy, the same time as did our contraction of the spleen.

Regulation of the Quality of the Blood. As Regards the Blood Count. Many observers now have studied the effect of contraction of the spleen upon the blood count—a problem which has been attacked in more than one way. The most direct attack was that of Cruickshank,¹⁹ who in the cat cut the splenic nerves and by tying nearly all of the anastomatic vessels reduced the lienal circulation to almost a simple system in which the blood entered the organ by the splenic arteries only and left it by the splenic vein only. He could then rapidly clamp the splenic artery, stimulate the splenic nerve and, collecting the blood which was evacuated from the spleen, determine its hemoglobin content. To give an example in which stimulation yielded 8 cc. of blood from the cat's spleen, the following were the hemoglobin values of each cubic centimeter, that of the arterial blood being taken as 100:

Cubic centimeter:—1st	2d	3d	4th	5th	6th	7th	8th
Hemoglobin value . 100	104	120	135	126	..	108	96

These results show at a maximum an increase of 35 per cent in the red corpuscles and on the average about 15 per cent. The addition of 8 cc. of such blood to that of the whole animal would not appreciably alter the erythrocyte count of the blood in the general circulation.

The above results fall far short of what might be expected from the experiments of numerous investigators who have produced indirect evidence of the effect of the splenic contraction on the red blood count. Their procedure has been to institute some experimental condition, asphyxia, adrenalin injections, exercise, etc., observe the consequent rise in the blood count and compare the results with that produced on a control splenectomized animal.

The most complete of such experiments are perhaps those of Scheunert and Krzywanek²⁰ who showed that the red count in the horse may rise from 6.01 million to 8.04 million on work. This means a 33 per cent increase in the red blood corpuscles. I cannot see how that could be effected solely by the spleen, even if the spleen contribution was 100 per cent corpuscles. Moreover, everything that we know about the mechanism of the body suggests that too large an alteration is only likely to be affected as the result of a combination of causes working in unison. Every adaptation is an integration.

Binet and his school have carried out a great many experiments

of this type of which the following by Binet and Williamson²¹ is a fair example:

	Red blood cell in millions per c.mm.
Dog-chloralose:	
Normal before asphyxial crisis	7.4
Normal after five minutes asphyxia	8.6
Normal before second asphyxia	7.7
Normal after five minutes asphyxia	8.4
Dog-chloralose:	
Normal before first asphyxial crisis	8.0
Normal after five minutes asphyxia	9.8
Splenectomized before second asphyxial crisis	8.8
Normal after five minutes asphyxia	8.8

In a form of life so widely different from the mammals as the dogfish, Hall and Gray²² have observed what appears to be essentially the same phenomenon. Reduce the oxygen content of the water in which the fish is contained, the spleen contracts and the red blood corpuscle count rises.

The question naturally arises, can such result be obtained on man? Himwich and Barr²³ in 1923 showed that exercise in man raised the oxygen capacity of the blood; these observations have been confirmed by the subsequent work of Harrison, Robinson and Syllaba.²⁴ Pickering and Syllaba²⁵ have, however, tried the same experiment on a number of splenectomized persons, in whom they also obtain an increase in oxygen capacity. If there is any difference then between the normal and splenectomized individuals it is at most a small differential one.

Iron. One of the striking appearances exhibited, especially by unstained sections of the spleen, is that of a brown material known as hemosiderin. A good deal of controversy has taken place about this substance, first as to whether it is always in cells or is sometimes free, and second, as to whether it is a compound more or less on the hematin level, as opposed to a compound of iron of a more-simple nature. As regards the first point, I can offer no opinion. I have certainly seen it outside actual cells, but whether or not the cells which may have contained it broke down in the processes to which the sections were treated, I am unable to say.

As regards the nature of the pigment, it must be admitted that, as usually found, it does not give the usual tests for inorganic iron such as those with potassium sulphocyanate, potassium ferrocyanide or potassium ferricyanate. It does, however, give a black coloration with ammonium sulphate. The recent work of Stanley Cook²⁶ seems to indicate that in spite of these facts, hemosiderin is nothing more complicated than ferric hydrate, but in some sort of colored suspension. Hemosiderin is seen not only in the spleen pulp, but often in large quantities in the sinuses which go to form the confluent of splenic vein and in the splenic vein chiefly it follows that when the spleen contracts such hemosiderin (that is, $\text{Fe}_2(\text{OH})_6$) as may be in the venous sinuses and the vein itself is driven on.

What becomes of it is as yet unknown. Nor is it known whether the number and strength of the splenic contractions have any influence on the rate of the production and, therefore, over any long time of its elimination.

The Fragility of the Red Corpuscles. Orahovats,²⁷ using essentially the same preparation as Cruickshank had done, studied the relative fragilities of the red blood corpuscles which enter and leave the spleen and obtained positive results. To graduated salt solutions, the corpuscles in the blood squeezed out of the spleen are more fragile than those of the general circulation. The interpretation of this observation is not very easy. One or both of two reasons might be ascribed. First, residence in the spleen might increase the fragility, or second, the spleen might filter off the more fragile corpuscles. As between these two views, the evidence which he adduced seemed to favor that which seemed inherently least likely, namely, that the spleen exercised some kind of selection, and the facts would be explained if we assume that in proportion to its fragility the corpuscle has a greater chance of sticking in the spleen.

Though these experiments were suggested to us by those of Pearce, Krumbhaar and Frazier, who showed that the fragility of the corpuscles varied for some time after the spleen had been cut out, and though our results are what might be expected, they will, I think, agree with me that the ultimate interpretation of both is not at all certain.

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THE AGRANULOCYTIC BLOOD PICTURE IN CONDITIONS OTHER THAN ANGINA.

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SINCE 1922, when Schultz called attention to the condition, an increasing number of cases of so-called agranulocytic angina has been reported, both in Europe and in this country. The picture painted by Schultz was characterized by the occurrence, usually in elderly females, of a necrotizing throat infection, with fever, rapidly developing exhaustion, slight jaundice and a quickly fatal issue with the blood picture of leukopenia, an almost complete absence of granulocytes, and almost complete lack of involvement of the red cells and platelets.

Since Schultz's article appeared, it has become apparent that all cases do not conform strictly to his original description. In some, contrary to his specifications, hemorrhagic symptoms have been present and in others involvement of the red cells with pronounced anemia has occurred. It has become clear that the necrotizing process does not necessarily involve the throat but that the gums, the esophagus, the intestines, the genitalia and even the skin may be attacked.

It is the purpose of this paper to point out that local and general sepsis not affecting primarily the skin or mucous membranes may be accompanied by a leukopenia and an agranulocytic blood picture and to discuss the differentiation of these conditions from others which may simulate them.

While four cases have been observed, only one came to autopsy. A brief description of this case, observed on the service of Dr. Francis G. Blake in the New Haven Hospital, will serve as a point of departure.

Case Report. C. M., a Scandinavian loom mechanic, aged fifty-two years, entered the medical service of the New Haven Hospital June 25, 1928, having been referred there for the treatment of glycosuria.

His chief complaint on entrance was lung trouble and weakness.

He stated that for three weeks before entrance he had been unusually fatigued, and that during this period he had lost 15 pounds in weight. He had also had a series of boils on his forearms. Two weeks before entrance he developed a cold, with chilly sensations, cough, slight dyspnea and purulent morning expectoration. There was anorexia and nausea, but no vomiting. He was constipated.

The past history was quite eventless. He had had the usual minor ailments of childhood but had never been sick since. There was no venereal or alcoholic history. There had been no serious injuries or operations.

His family history was without significance. His parents died at an advanced age and he had five healthy children.

On entrance to the hospital he had a temperature of 100° F., a pulse of 88 and a respiration of 20 to the minute. He was poorly nourished and his skin was sallow, subicteric. The teeth showed caries and there was an area of reddened, swollen and slightly tender gum where a tooth had been removed several weeks previously. The chest was noted to be emphysematous but the examination of the other organs showed nothing of note.

The urine had a specific gravity of 1012, showed the slightest possible trace of albumin, no sugar and was otherwise normal.

The blood, June 25, showed red blood corpuscles 3,100,000, hemoglobin, 60 per cent, leukocytes, 2600. The differential count, stated in the history to be probably incorrect, showed polymorphonuclears, 61 per cent; lymphocytes, 39 per cent, large mononuclears, eosinophils and basophils none. The appearance of the red cells was said to be normal.

June 27. The leukocyte count was 1600, with a differential count of polymorphonuclears, 54 per cent and lymphocytes, 46 per cent.

June 28. The leukocytes were 1800.

On June 29 swelling of the left thigh with fluctuation was noted. The patient left the hospital against advice on this date.

July 14 the patient returned to the hospital with swelling and tenderness of the left thigh. He had been in bed since his return home and had developed during that time a second tooth abscess which ruptured spontaneously.

He was transferred to the surgical department of the hospital where a large abscess of the thigh was opened and drained. Cultures from this showed *Staphylococcus aureus*. He was noted at this time to be subicteric with negative heart and lungs, a liver palpable at the costal margin and no enlargement of the spleen. There were a few palpable posterior cervical lymph nodes.

A blood count July 15 showed: red cells, 2,500,000; hemoglobin, 75 per cent; leukocytes, 4250. The differential count showed polymorphonuclears, 2 per cent; lymphocytes, 36 per cent; large mononuclears, 62 per cent. The Wassermann reaction was negative.

Three blood cultures were taken which all showed different organisms. The first, *Staphylococcus albus*, the second a Gram-negative bacillus, the third *Bacillus pyocyaneus*. These were probably all contaminations. He ran a moderate fever, and never showed any splenic or glandular enlargement. There was no marked change up to the time of the patient's death, July 29, 1928.

Further blood counts: July 16. Red blood cells, 2,200,000; hemoglobin, 75 per cent; leukocytes, 3000.

July 24. Red blood cells, 2,600,000; hemoglobin, 75 per cent; leukocytes, 2000. Differential polymorphonuclears, 5 per cent; atypical mononuclears, 95 per cent.

Autopsy was made by Dr. George Wilson two hours after death. Anatomical diagnosis:

Primary. Hyperplasia of the bone marrow, generalized lymph node enlargement, splenomegaly, acute gingivitis, multiple petechial hemorrhages into the submucous and subserous surfaces, focal necrotizing pneumonia.

Subsidiary. Ulcerative periostitis of the left femur, hydrocele of the right testis, fibrous thickening of Glisson's capsule.

The microscopic examination did not show the usual lesions of lymphatic leukemia. There were no accumulations of lymphoid cells in any of the viscera. The bone marrow was hyperplastic. Megakaryocytes were scattered through the tissue and normoblasts were present, but the tissue was predominantly made up of agranular leukocytes and embryonic white blood cells.

In summary, then, a man, aged fifty-two years, with a negative family and past history developed an illness characterized by the occurrence of root abscesses in two teeth, exhaustibility, cough and expectoration, anorexia, fever, loss of weight and an ulcerative periostitis of the thigh. Physical examination showed no clinical enlargement of the spleen or lymph nodes, a palpable liver, and a blood picture of moderate anemia with marked leukopenia and almost complete absence of granulocytes. Death was apparently due to sepsis, exhaustion and a terminal focal pneumonia. The postmortem examination showed a hyperplastic bone marrow but did not show the usual histologic picture of lymphatic leukemia.

An examination of the literature shows that somewhat similar cases have been reported from time to time for over twenty years.

In 1904, Schwartz¹ reported the case of a boy, aged nine years, with a renal or perinephritic abscess which ruptured into the urinary tract. There was improvement for a time but after several weeks the boy developed gingivitis, swelling of the submaxillary glands and a leukocyte count of 600, the differential count showing no polymorphonuclear cells. Only a brief abstract of his paper is available and the report is not entirely satisfactory.

Türk,² in 1907, reported a case of staphylococcus sepsis with peculiar changes in the blood and bone marrow. The patient, a previously well woman, aged forty-five years, developed general malaise, pains in the right flank and cough. Later fever with chills, headache, anorexia and still later diarrhea occurred. There was high fever, stupor, an embolic skin eruption, a mitral murmur, a patch of consolidation in one lung, and a few slightly enlarged lymph nodes. There was some ulceration of the lips and in places necrosis of the gums. Before death, which occurred about a month after the onset of the illness, the spleen was palpable, the sternum and ribs were tender and the tonsils were covered with an opaque white membrane. The blood on entrance showed 5,245,000 red cells, 92 per cent of hemoglobin and 940 leukocytes. Of the leukocytes 93.5 per cent were lymphocytes, 4.4 per cent large lymphocytes, 0.6 atypical mononuclears, and 1.5 per cent basophils. The platelets were slightly increased. There were slight changes in size and shape of the red cells. A subsequent differential count showed 96.1 per cent lymphocytes, 2.23 per cent large mononuclears, and 0.55 per cent basophils. Cultures from the skin lesions showed *Staphylococcus aureus*. A blood culture was negative.

The autopsy showed sepsis with fresh endocarditis, lung abscess, and no evidence of leukemia either in the gross or in sections. *Staphylococcus aureus* was recovered from the blood. The bone marrow appeared normal except for small hemorrhagic areas. Microscopically, most of the white cells in the marrow were lymphocytes and plasma cells.

In 1912, Stursberg³ published a paper on the differential diagnosis

between acute leukemia and sepsis. He cited the case of a husky blacksmith, aged forty-one years, who, in 1910, was operated on for osteomyelitis of the arm. In the fall of 1911, he developed bleeding from the nose and mouth, increasing pain in the mouth and dysphagia. Examination showed swelling of the cheeks with a brownish-red discoloration of the mucosa and swelling of the tissues of the face and neck. There was fever. The spleen was not felt and the internal organs showed no demonstrable change. There were numerous petechiæ and suggillations on the legs. The patient died the day after admission. The leukocyte count was 900 and no granular cells were seen in counting 408 leukocytes. There were 399 lymphocytes, 8 large mononuclears and 1 lymphoblast. The red cells showed no change in morphology.

The autopsy by Ribbert showed nothing of moment. The spleen was not enlarged. The long bones showed fatty marrow. There was no sign of leukemia either in the gross or microscopically. The erythroblastic part of the marrow was unaffected.

In 1913, F. Marchand⁴ reported the case of a man, aged twenty years, with weakness, increasing pallor and bleeding from the gums. There were small bloodclots on the lips and blood on the posterior pharyngeal wall. The lymph nodes in the neck, axillæ and groins were slightly enlarged. The heart was slightly enlarged and showed a soft systolic murmur. The liver was slightly and the spleen markedly enlarged. There was blood in the stools and retinal hemorrhages. The urine contained albumin and urobilin.

The blood showed 1,500,000 red cells; hemoglobin, 35 per cent and 2100 leukocytes. The differential count showed polymorphonuclears, 6.5 per cent; transitionals, 8 per cent and lymphocytes, 85.5 per cent. Death occurred after an illness of about a month with a clinical diagnosis of acute lymphatic leukemia.

The autopsy showed no signs of leukemia. The long bones contained fatty marrow. The organs showed hemorrhages. There were small, nonsuppurative embolic lesions in the lungs and brain. Those in the lungs contained streptococci. It was a case of pyococcal sepsis with agranulocytosis.

In a paper on lymphocytosis published in 1928, Kenneth McAlpin⁵ records the case of a child, aged three years, with a history of fever of five months' duration. He had slight swelling of the face, swollen lymph nodes and a marked anemia. Some of the nodes in the neck were incised and *Staphylococcus aureus* was obtained. The internal organs showed no demonstrable clinical change. The leukocytes on admission were 2100 with 32 per cent polymorphonuclears, 65 per cent lymphocytes, and 3 per cent mononuclears. His final count showed 1200 leukocytes of which 8 per cent were polymorphonuclears, 68 per cent lymphocytes, 12 per cent mononuclears and 12 per cent smudges. A blood culture shows *Staphylococcus aureus* and the postmortem showed innumerable abscesses in the viscera.

It is evident that in this group of patients, as in those with agranulocytic angina, we are dealing with individuals whose bone marrow reacts differently to bacterial infection than does that of most patients. It can hardly be argued that this peculiarity in reaction is an inborn permanent condition, for in agranulocytic angina, where a much larger number of cases is available for study, there are instances where the same patient has reacted with the usual polymorphonuclear increase to one attack of an infection and has shown an agranulocytic reaction to another attack. It is a moot question, on which there is a good deal of disagreement, whether the bone marrow condition precedes the local infection or follows it. If it is assumed to precede it, and certainly in some cases the patient is ill before the development of local lesions, we are only pushed a step farther back for we must then account for the condition of the bone marrow. Something, perhaps some toxin, damages the bone marrow in such cases and paralyzes its ability to form granulocytes. It is natural to think of this action as a toxic one from analogy to the known effects of chemical substances such as benzol, thorium and other agents on the bone marrow. There is evidence in some cases, on the other hand, that in the early stages of the infection there is still granulocyte formation and that the agranulocytosis becomes more and more pronounced as the infection progresses. This suggests the infection as the cause of the bone-marrow lesion. There is, of course, evidence in the cases that recover that the damage to the bone marrow is not permanent and irreparable. In the present state of our knowledge this question must be left open.

From the point of view of diagnosis, sepsis with agranulocytosis raises great difficulties, chiefly because certain blood diseases such as leukemia and aplastic anemia, in which there is also agranulocytosis, are frequently accompanied by terminal infections, especially about the mouth and throat.

So far as acute leukemia is concerned I feel that we must agree with Stursberg and Marchand that a diagnosis during life between the so-called aleukemic type of lymphatic leukemia and sepsis with agranulocytosis is not possible. I am aware that some observers claim to be able to make a differentiation on the morphology of the blood but I doubt this. A final decision can only be reached in the pathologic department.

With aplastic anemia, the difficulty of diagnosis is not so great, at least in typical cases. In agranulocytic sepsis, the power of the marrow to form red cells is often but little damaged, so that the very low red blood counts usually observed in aplastic anemia are not found. The leukopenia and agranulocytosis are common to both diseases. Nevertheless recent experience has led to the conclusion that there are patients with an aplastic type of anemia of obscure origin, that is, not obviously secondary to a known toxemia, who may have a fairly high red blood count and there are patients

with an agranulocytic infection who may have quite a low red blood count. The subject is one which demands further critical study.

Conclusions. 1. There are cases of local and general sepsis with an agranulocytic blood picture, aside from the well-recognized group of agranulocytic anginas.

2. It is not yet clear whether the sepsis or the loss of power of the bone marrow to form granulocytes is the primary lesion.

3. Such cases cannot be differentiated clinically from acute aleukemic lymphatic leukemia with terminal infectious processes.

4. In some instances it may be difficult to differentiate them from aplastic anemia with terminal infection.

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ANGINA PECTORIS; IS IT ALWAYS DUE TO CORONARY ARTERY DISEASE?*

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ANGINA pectoris is a clinical syndrome with no definitely recognized pathology and as such its limits are difficult to state and so there may be doubt as to whether a given case should be so designated. However, there are certain features which are usually regarded as characteristic in a general way: (1) There is severe pain which is referred to some part of the sternum or beneath it. (2) There are certain common causal features, exertion, emotion or anger, a heavy meal (especially with any of the other factors) and exposure to cold. (3) There is an immediate enforced cessation of activity. (4) The pain tends to radiate. (5) Sweating is common. (6) The attack is relieved by rest, nitrites and morphia. (7) The patient is usually in his normal state within a few days at most.

Recently there is an increasing tendency noted in articles to consider that these symptoms are due to coronary artery disease exclusively and the possibility of any other cause is regarded as out of consideration. With this in some cases has been the inclusion of the features of acute coronary artery occlusion as a special form of angina pectoris. This seems to be unfortunate, as it tends to put under one heading a condition with definite clinical features and a

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positive lesion with a group which is much less definite. In one condition there is a syndrome (angina pectoris) with uncertainty as to the cause in some cases, without a definite pathology and with an uncertain outlook. In the other (acute coronary artery occlusion) there is a very definite etiology and pathology with a prognosis which can be reasonably estimated. The treatment of the two conditions differs in many respects. Is it wise to group them together?

I speak of frank coronary artery occlusion and not of coronary artery disease in general, or of what may be termed slight chronic occlusion. My feeling is that there are a number of causes of angina pectoris, of which cardiac disease is one but not the only one. If we regard these symptoms as always due to coronary artery disease, with which I am specially concerned, or its effects, how are we to explain the following groups of cases? I quite realize that one case may prove nothing but it can raise doubts.

1. *Angina Pectoris and Coronary Artery Occlusion in One Patient.* A man, aged sixty years, who led a high-pressure life, for two years had attacks of angina pectoris. He had moderate arteriosclerosis, no evidence of renal disease, had not had syphilis, and usually had a blood pressure of 150 to 160 systolic and 90 diastolic. He was given to fits of anger on slight provocation. On the day on which I first saw him, when coming to my office his motor was struck by another car and while no great damage was done he became very angry, so that a severe attack of angina pectoris began and was well developed on his arrival. He showed the usual picture with a gray look, severe suffering and profuse sweating. The pulse and blood pressure showed no change. He was relieved rapidly by nitroglycerin and morphia. His pain was referred to the upper sternum and radiated into the neck and down the left arm. He outlined the situation of the pain very definitely and was emphatic that it was never over the lower sternum or precordium. Afterward he said that he expected death in each attack. He went on reasonably well if he took care for about two years. Then came a different attack in the form of an acute coronary artery occlusion. He was not far from the hospital where he was brought at once and I saw him a few minutes later. The picture was definite, with severe pain referred to the lower sternum and both sides of it, marked collapse, a rapid feeble pulse, a blood pressure of 90 systolic, with the diastolic difficult to determine. Later he had fever and a pericardial friction rub. After this he was an invalid and died about six months later. He did not have another attack of what I regarded as angina pectoris. Of course, he was quiet and there was no overexertion but there were fits of anger.

Here is the point of particular interest. After he had recovered somewhat from his attack of acute coronary artery occlusion, he volunteered the statement that this attack was different from any

he had before, with a different situation and a different pain. When asked how the pains differed he said "I cannot describe these pains but they are not the same. You cannot describe the difference between the taste of a strawberry and a pineapple."

In another patient there was much the same story. I did not see him in any of the angina pectoris attacks but his physician had seen him in several and the description left little doubt of their nature. I saw him in an attack of coronary artery occlusion. He also was very emphatic in his statement that the pains were different in character and situation. In his earlier attacks the pain was felt below the upper sternum; in the coronary occlusion attack beneath the lower part of the sternum.

Another example of pain of different situation was seen in a young adult who had syphilitic aortitis and also syphilitic myocarditis. I am aware of the difficulty of being certain of the latter, but this diagnosis was apparently justified. The patient volunteered a description of two kinds of pain, one felt under the upper sternum, the other under the lower sternum and to the left. The pain which we regarded as due to the aortic disease, referred to the upper sternum, was the more severe and brought on by very slight exertion. It occasionally came on without any evident causal factor. She did not have attacks which we regarded as angina pectoris.

A few patients regarded as having angina pectoris have described two varieties of pain, one referred to the upper sternum and the other referred to the lower sternum and precordium. One patient, who had marked dilatation of the aorta and whose symptoms dated back for three years, stated that it was the pain felt over the upper sternum which radiated down the left arm; the lower sternal pain never did. My suggestion is that the upper sternal pains in these patients were due to aortic disease.

2. *Duration of Symptoms.* If all the features of angina pectoris are due to coronary artery disease what happens in the patients who have severe attacks for many years? If each attack of angina pectoris is due to something occurring in the coronary distribution, perhaps in a very small branch, there hardly seems enough vascular territory to supply sufficient material. An example is as follows: A physician had his first severe attack of angina pectoris in 1896 and was seen by Sir William Osler, who told me that he did not expect him to recover. He went away for a long rest and afterward resumed his work. He recognized his limitations and did very well but emergencies were very apt to bring on an attack. Exertion beyond a certain point always did so and he knew very accurately how much was safe. He had often spoken to me of his symptoms but first consulted me in 1910. His attacks were the most severe that I have ever seen. The pain was first felt in the back and "came through," as he expressed it, to the front. He could not localize the pain exactly; it was felt over the greater part of the

sternum and to the left. There was intense suffering. He threw himself on his back, stretched his arms out at right angles to his body and very quickly took the position of opisthotonos, resting on his head and heels. Morphia gave prompt relief. Nitroglycerin had done so before but had lost its effect. As a rule the pulse rate remained at 72; the highest in any attack which I saw was 84 for a very short time. The heart showed no particular change and the blood pressure hardly altered from a systolic figure of 140 and a diastolic of 90. He died in an attack.

Over a period of fourteen years this patient had many attacks, not all of maximum severity, although the majority were severe. He died without any evidence of serious cardiac change. Could all these attacks have been due to coronary artery disease? They may have been due to spasm but, if this was marked, why was there not more change in the action of the heart?

3. *The Group Associated with Esophageal or Gastric Symptoms.* This group is one which has puzzled us all, I am sure. An example is under observation at present. The patient, aged sixty-seven years, is well preserved, with moderate arteriosclerosis and a heart which shows no particular evidence of disease. His attacks have occurred for a period of four years and as a rule begin with a feeling of gastric distention and a desire to belch, soon followed by pain. Years ago he had done gastric lavage himself for indigestion and it occurred to him that if he passed a stomach tube at the first sign of any distress he might obtain relief. His idea was correct but some one told him that it was dangerous and it was regarding this that he consulted me. I advised him to continue with it and for three years he has been able to prevent every attack becoming severe with one exception. This began when he was unable to get his stomach tube promptly and was severe, requiring morphia and nitroglycerin. He is careful with regard to diet and overexertion, but the effect of the passage of the stomach tube in cutting short an attack seems well established.

How are we to regard such a case? If due to reflex spasm of the coronary arteries, one might suppose that the relief of gastric distention could be responsible, but it does not seem likely that a patient, aged sixty-seven years, has coronary arteries which are capable of much spasm. If there is some change, such as occlusion of a very small branch, how can his procedure influence this? The reverse may occur. In one of my patients the first attack of angina pectoris came on while a biliary drainage was being done. There are some cases apparently secondary to gall-bladder disease in which after removal of gall stones the attacks of angina cease. What is the mechanism here? You may suggest coronary spasm but it is about as easy to deny as to assert its probability. I recently saw a remarkable case with my associate, Dr. Martin Rehfuess, whom the patient consulted for difficulty in swallowing.

He was given barium and while Dr. Relfuss was examining him before the screen there was a sudden esophageal spasm with spasmodic contractions. The patient made severe efforts to belch without success and then suddenly a very severe attack of thoracic pain began.

4. *Angina Pectoris Apparently Secondary to Disease Elsewhere.* A man, aged forty-seven years, came with a history of two years of attacks of thoracic pain which were growing more frequent and more severe. He had seen a number of consultants who agreed on the diagnosis of angina pectoris. He had read extensively about it, had made up his mind that "Death was just round the corner waiting for me" as he put it and expected each attack to be his last. Examination showed no evidence of any disease of the circulation but there was evidence of a severe prostatitis and inflammation of the verumontanum with marked tenderness. Treatment of this was begun at once with rapid improvement in his general condition and a gradual disappearance of the attacks of thoracic pain. That is twelve years ago and he has remained free of the symptoms of angina pectoris ever since.

How is one to explain such a case as this? Clinically, there seemed no question of the character and severity of the attacks. His physician had seen him in a number of them and stated that he had expected him to die in several of the attacks. His wife gave a very graphic description of them. Were they due to coronary spasm or to spasm of the aorta? Was there some definite change in a coronary artery with each of them? The last is difficult to believe. This case suggests that a purely nervous mechanism may be at work. In recent literature this possibility receives scanty attention but it appears to be the most reasonable explanation for some cases. The studies of Libman on the individual variations in response to pain must be remembered in this connection. There is also the group in which the first manifestations of an attack are in the periphery, for example in the arm. Later there is substernal pain.

5. *The Influence of Myocardial Insufficiency on Angina Pectoris.* The usual rule is that when symptoms of myocardial insufficiency appear, the attacks of angina pectoris stop. This is not invariable, as in one patient who was seen in several attacks of angina pectoris, which did not begin until after the onset of decompensation. His pain was always felt beneath the upper sternum. If the myocardium struggling to work with an insufficient blood supply and anoxemia are essential and invariable factors in the causation of angina pectoris, why should this be? The patients who have had angina pectoris and then a frank coronary artery occlusion do not seem to have any more attacks of the former after the latter has occurred.

6. *The Occurrence of Angina Pectoris in Patients with Dilatation of the Aorta.* As a rule the attacks of pain in these patients do not

have the usual characteristic features of angina pectoris but some of them do. The pain is referred to the upper sternum and may radiate down both arms or down the right arm only.

These points may be regarded as of small importance when taken singly, but considered together it seems to me that they present a strong argument against the syndrome termed angina pectoris being always due to coronary artery disease or necessarily to heart disease of any kind. You may say that the question has been asked but not answered, and I agree, but these points seem arguments against an exclusive coronary artery etiology.

The use of the term angina pectoris, with our present knowledge, cannot be governed by set rules, but the majority of us would agree that it is a combination of clinical features which are fairly definite. The pain may be felt beneath any part of the sternum, but I should insist on the importance of the relationship to the sternum. Pain felt about the apex of the heart only is probably not due to angina pectoris. Angina pectoris may appear later in such a case.

There are possibilities of many variations and differences in the several features. We would agree that while we may sometimes be in doubt from a patient's description of his attacks, there is rarely any question if we witness an attack. Is it not a mistake to include under this syndrome with its uncertainties such a definite picture as is presented by acute coronary artery occlusion? Why put a clear-cut entity into an indefinite group when it has been separated after many years of confusion? We all agree that many cases previously regarded as angina pectoris are due to coronary artery occlusion.

As to the factors which cause angina pectoris, it seems most reasonable to regard it as having a multiple etiology. Disease of the aorta in some cases, of the coronary arteries and myocardium in others, probably of both in some cases, seems definitely established. That other causes may operate seems probable in the way of viscerosensory reflexes. May these represent spasm largely? It may be entirely possible but the possibility of a nervous mechanism alone should not be entirely neglected.

Summary. 1. Angina pectoris is a clinical syndrome with fairly marked features but without any definite single causal pathologic change. It should be clearly distinguished from *acute* coronary artery occlusion which has a definite pathologic basis.

2. The statement, frequently made, that angina pectoris is always due to coronary artery disease does not seem to be supported by the evidence. The same may be said of the view that it is always due to a "tired heart muscle."

3. There are probably several factors which may be operative in causing an attack, in the aorta, in the coronary arteries and myocardium and in the nervous system. It is doubtful if disease of any one structure can explain all cases.

THE INVOLVEMENT OF THE CORONARY ARTERIES IN RHEUMATIC FEVER.

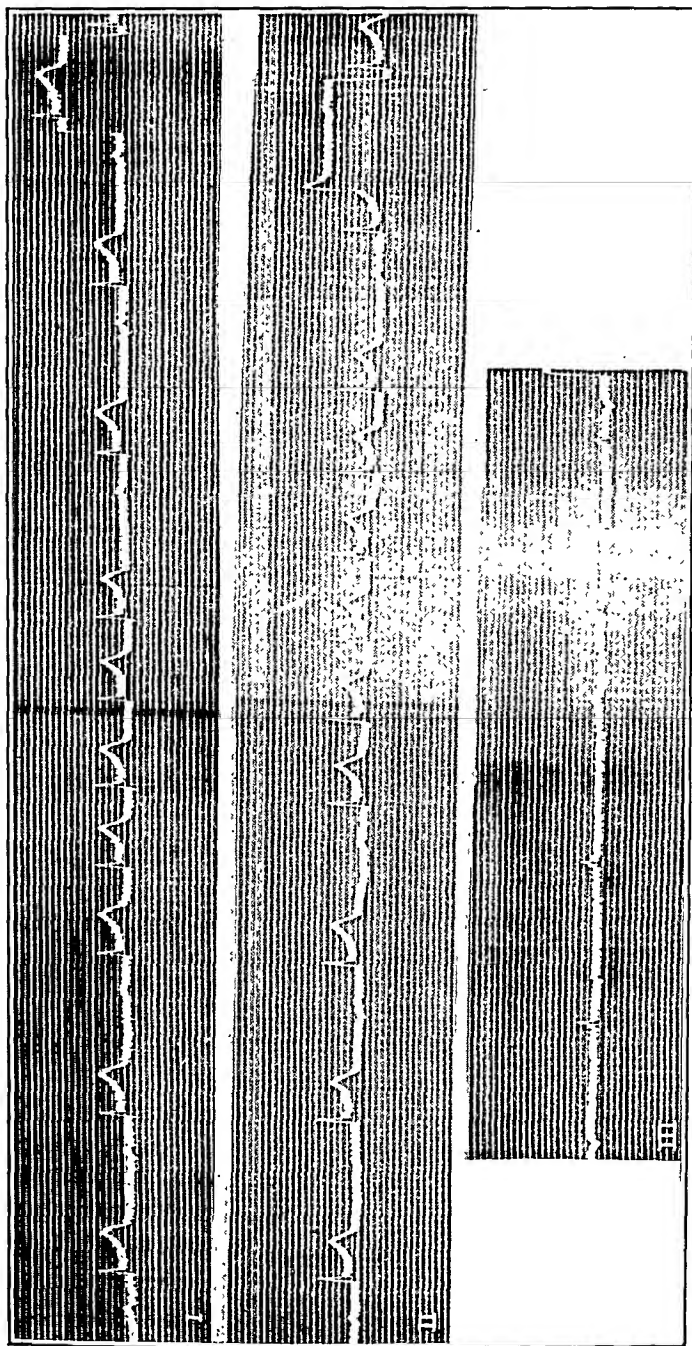
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OUR interest in the specific changes in the vascular system in rheumatic fever particularly as affecting the coronary vessels was stimulated by the case to be cited. This case occurred in the wards of the Jewish Hospital of Brooklyn, N. Y., on the service of Dr. Alex L. Louria. It is with pleasure that I acknowledge my thanks to him for the privilege of reporting this case and his many kindly suggestions.

Case Report. M. G., female, aged thirty-six years, married, was admitted on January 10, 1928. Her previous history was unimportant except to note that she had been admitted three times previously for surgical conditions at which times no subjective or objective cardiovascular symptoms were demonstrated. In June, 1927, six months prior to admission, she began to complain of slight dyspnea, precordial distress, epistaxes, weakness, pallor and a progressive loss of weight (20 pounds). On January 7, 1928, she was suddenly seized with extremely severe pain in the epigastrium radiating to the right anterior chest and right arm, relieved only by large doses of morphin. On admission, she was dyspneic and vomited, and on examination was in shock and in great pain; there was an anxious expression on her face, her forehead was covered with cold perspiration, her throat was congested. Her pulse was irregular and slow, 48 per minute, the heart sounds were of poor quality and the heart was moderately enlarged. A diagnosis of coronary closure with partial heart block was made. The next day an enlarged tender liver was noted, a localized friction rub appeared to the left of the sternum, and concomitantly a leukocytosis and a moderate temperature developed. From then on to January 21, 1928, she ran an irregular temperature, with frequent nosebleeds, fugacious pain and swelling of the various joints. These subsided promptly on the administration of salicylates. She felt well until January 25, 1928, when again her temperature rose, nosebleeds recurred and her joints were again successively involved. The response to salicylates was again prompt. On the last day of January, 1928, her temperature was normal. A soft systolic murmur had appeared at the apex, the heart was widened. She felt well until February 21, 1928, when she again developed repeated epistaxes, an acute follicular tonsillitis, following which her joints again became swollen and tender. Her temperature again rose, varying between 101° F. and 103° F. This lasted two weeks, the symptoms being relieved by salicylates. Blood cultures, chemistry of the blood and Wassermann reactions were negative. The electrocardiogram at the time of her admission showed the *T* waves coming off midway on the down limbs of *R* in Leads I and II (see illustration). Later electrocardiograms showed the gradual inversion of the *T* waves which in later tracings became upright.



The large T waves of Leads I and II come off almost midway on the down limb of the R waves. The T of Lead I is frequently higher than the R and almost as high as the R of Lead II.

Discussion. The history for six months before her last admission was such as to suggest to us invasion of the myocardium by the rheumatic virus. Suddenly, three days prior to her admission, she developed a coronary occlusion. The electrocardiogram showed the findings we recognize as occurring in closure of a large branch of the coronary artery.^{1, 2, 3, 4, 5} That no such electrocardiographic finding as that illustrated occurs in uncomplicated rheumatic fever has also been demonstrated (Parkinson, Gosse and Gunson,⁶ Cohn and Swift,⁷ Bain and Hamilton,⁸ Donner,⁹ Bezancon and Weil¹⁰ and Rothschild, Sacks and Libman¹¹). Furthermore the *T*-wave changes were identical to those produced experimentally by F. M. Smith,^{1, 2, 3} when he tied off branches of the coronary artery. We felt, therefore, warranted in our diagnosis of occlusion of the coronary artery. Embolization was ruled out by the physical examination which eliminated mitral stenosis, subacute bacterial endocarditis and thrombophlebitis, and the negative laboratory data. What interested us was the relation between the closure and the typical attacks of rheumatic fever during which this apparent closure occurred. We assumed the direct bearing of the rheumatic infection on the production of the latter.

Quite early the French mentioned changes which occur in the vessels in rheumatic fever (Hayem,^{12, 13} Martin,^{14, 15} Landouzy and Siredey,^{16, 17} Huguenin.¹⁸ Later Krehl¹⁹ and Cowan²⁰). In 1894, Romberg²¹ described extensive hyaline thrombus formation and intimal thickening and cited also a case report of Leyden.²²

Aschoff²³ states that all coats of small- and medium-sized arteries may be involved in the process of submiliary nodule formation. Aschoff and Tawara²⁴ say "aside from these last changes, healing of the arteritic and periarteritic foci can cause such sclerotic narrowing that ischemic necrosis may result. At all events we believe that all scars are due either to plugging of vessel or anemic necrosis and not primarily to interstitial myocarditis." Aschoff^{25, 26} further says that this anemic necrosis plays a large part in the myocardial weakness in rheumatic fever. Giepel^{27, 28} tells of the presence of giant cells in the vessel walls and the lumina of small arteries. The nodules in the arterial wall may cause a real breach due to injury of the elastica and media. He cites a case where a man suddenly died while walking and in whose heart numerous nodules were found: "On the descending ramus of the left coronary artery the entire wall was penetrated in two places by the destructive process." In 1909, he²⁹ describes the process as beginning at the periphery and extending inwardly. Coombs^{30, 31} mentions arteritic and periarteritic processes occluding vessels, and emphasizes this in later writings,³² and again in his book.³³ Takayasu³⁴ found similar changes and noted crescent formation on cross section, due to wall infiltration with new tissue showing a granular structure in which endothelial cells were embedded, giant cells present and at times thrombi seen.

These sections followed serially showed they represented a lengthwise stenosis of a portion of the artery. Wätjen³⁵ reported an unusual case of recurrent rheumatic infection in a man aged fifty years. The heart showed old healed scars and fresh infarcts, with nodules invading the walls of the vessels. When the nodule was not present, the wall was invaded by eosinophilic leukocytes and the lumen filled with either fresh thrombi or older organized tissue, partially or completely closing the lumen. The nodule may form in any layer of the artery and produce the clinical condition he termed arteritis nodosa rheumatica. Gerhardt³⁶ cites a closure of a small branch to the conducting system in rheumatic fever. MacCallum³⁷ says involvement of the coronary system is not very common but does occur.

Swift³⁸ states "changes in the bloodvessels are common. Not infrequently one encounters complete or partial closure of the lumina with thrombi that have formed as a result of injury to the vessel. The bloodvessel may be constricted in other ways. Compression may be due to nodule in the perivascular space. Endarteritis with swelling and proliferation of the endothelium is not infrequently encountered in the smaller branches of the coronary arteries. Interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of impulse conduction." Sacks,³⁹ in discussing the vascular changes, quotes Libman⁴⁰ and Hess⁴¹ who speak of thrombosis in veins as well as other arteries.

Recently, von Glahn and Pappenheimer⁴² described specific lesions of the peripheral bloodvessels and in 1927 these authors⁴³ showed the widespread extent of the involvement of the vascular system in rheumatic fever, changes being described in the large vessels, notably the aorta, resembling the accepted rheumatic lesions, namely verrucæ and Aschoff bodies. That the intima of the large vessels such as the aorta, pulmonary, innominate and carotid arteries are frequently involved has, however, long been established, Jores,⁴⁴ Stumpf,⁴⁵ Reiche,⁴⁶ Heydloff.⁴⁷

The review of the literature indicates that rheumatic fever frequently involves arteries of various sizes. Our interest is concerned in the specific involvement of the coronary system. The coronary arteries may be involved directly as shown by the intimal changes or indirectly by the submiliary nodule. The earliest changes are those of proliferation of the endothelial cells. They begin to heap up but are not destroyed, fibrin is deposited beneath this layer, eosinophilic leukocytes may infiltrate the wall, but more often there is a small round-cell infiltration. The size of the artery seems to determine the further course. In the aorta structures like that of the nodule or even verrucæ may form. In the coronary arteries the subendothelial deposit may so lift up the endothelium that the lumen may be completely occluded, or the heaping up of the endothelium may be localized to one side of the vessel, and there may undergo

organization producing nodularity of the lumen. If the process goes further, necrosis of the media takes place and the elastic lamina now begins to share in the process. At this stage thrombosis may take place, though the formation of a thrombus does not depend on the degree of involvement of the vessel. Why in severe involvement no thrombosis may take place; and, on the other hand, will take place with a minimal or practically noninvolvement is hard to say; that there is another factor in the production of a thrombus is certain for it occurs rather frequently in rheumatic fever.

When the coronary artery is involved indirectly, it is by way of the Aschoff nodule which begins in the perivascular space or in the adventitia. This enlarges toward the media and the first result may be compression of the lumen and resultant ischemic necrosis. The nodule may involve the media and adventitia, producing a nodularity of the lumen. It may even cause a destruction of these coats and produce a breach in the wall of the artery. As can be seen, thrombus is a likely sequel. Healing takes place by fibrosis of the intima, producing irregularity of the lumen, or, if thrombus takes place, organization of it with recanalization.

Our case had a rheumatic involvement of her myocardium for six months prior to her admission during which involvement of the wall of a large branch of the coronary occurred. Suddenly thrombosis of this vessel occurred giving rise to the picture of intense angina, as noted also by Kaufmann,⁴⁸ Mönckeberg.⁴⁹

A consideration of the involvement of the coronary arteries in rheumatic fever suggests that the symptomatology resulting therefrom may be divided into three groups.

The first group is rare. It includes those cases in which a severe attack occurs during the course of the active stage of involvement of the myocardium in the rheumatic infection, due to involvement of one of the main branches of the coronary artery. It is due to involvement of a large branch of the coronary artery that sudden death may occur, as in the case of Giepel,²⁷ or thrombosis may take place, producing a severe attack of angina pectoris with recovery as in our case.

The second group includes those cases in which the symptoms are caused by the involvement of the coronary branches of small or medium size. This is the frequent or usual type. The symptoms may be of three kinds:

1. Pain. This is mild, variously described by the patients during the active stage of rheumatic fever as annoying, pinching, aching or scratching. If the vessels involved are near the pericardium, pericardial reaction and its type of pain is produced.

2. If the process is very extensive, the nutrition of the myocardium suffers and symptoms of cardiac embarrassment are produced; or, if previously present, aggravated.

3. If the nutrient vessels to the conducting system are occluded, various types of irregularity are produced.

The third group has been little emphasized and may more properly be regarded as a sequel. Healing as has been mentioned frequently takes place, producing fibrous nodularity of the lumen. This site may become the locus for arteriosclerotic processes. It is but another step for these patients to become the sufferers of angina pectoris. Patients who suffer from angina pectoris especially those of the fourth decade frequently give a history of rheumatic affection. This has recently been the subject of a paper by Kahn⁵⁰ who in 82 cases of angina pectoris was able to obtain a history of rheumatic fever in 20 and of recurrent attacks of tonsillitis in 28. This latter condition is interesting in the light of the observations of anginal attacks ensuing upon recurrent tonsillar infections and their cessation upon the removal of diseased tonsils (Louria⁵¹).

Summary. 1. A case of thrombosis of the coronary artery due to rheumatic disease with characteristic electrocardiographic findings is reported.

2. The symptomatology and pathogenesis of rheumatic coronary arteritis are discussed.

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THE CHANGING CLINICAL PICTURE OF LESIONS OF THE BREAST.

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THE clinician or internist today is called upon more and more by his patients to make a complete physical examination, and by his most enlightened clientele an annual periodical survey. In addition to this, due to the educational effort of the medical profession in this country, the majority of women no longer delay when their attention is called to the breast by any type of warning.

Up to 1900, and even up to 1910, in the ordinary physical examination, the breast received scant attention, even the thyroid area was usually overlooked, although the presence or absence of palpable glands in the neck, axilla, groin, supratrochlear area were usually noted in the histories. When women came to surgeons referred by their family physicians, with the rarest exceptions, the breast was the seat of a perfectly definite lump. My figures show that 80 per cent were cancer, and 20 per cent benign. Of the benign group in not more than one was operation not indicated. This has changed. My most recent figures are: 17 per cent malignant; 18 per cent benign, with definite lumps which were subjected to operation; and the remaining 65 per cent benign, in which operation was not indicated.

When the per cent of malignant lumps in the breast were 80, the inoperable group was 50 per cent or more, and the five-year cures 20 or less. When the per cent of malignancy in the entire group had been reduced to 20, or in the group in which operation

was performed, to 50, the inoperable group had fallen to less than 5 per cent, and the five-year group had increased almost to 60.

In former years it was minor diagnosis, major surgery and minimum results. Today, it is major diagnosis, minor surgery and maximum results. Today the first difficult clinical problem is to find by palpation the definite lump. The next is a surgical-pathologic problem to distinguish, in the fresh frozen section made in the operating room, the benign from the malignant.

There is, therefore, much that a surgeon and surgical pathologist (who has had the good fortune to live through this long period of thirty-nine years) has to tell his colleagues about the inspection and palpation of the breast in the routine physical examination and in the periodic examination, and in the enlightened group of women who seek his advice the moment they are warned.

There is, first, the inspection of the nipple for areas of keratosis and irritation which, if neglected lead to Paget's cancer of the nipple; the interpretation of the different types of retracted nipples and discharge from the nipple. Then there are the visible swellings in the axilla which are often aberrant breast tissue; the significance of pain in one or both breasts; its relation to definite pathologic processes in the breast, to menstrual periods, and to fear. It is well known that the two breasts of an individual differ in their size. They may even hang at different levels. It is not so well known that there are various types of breasts which give to the palpating finger different sensations—the breast of pregnancy is a little different from that at puberty; the lactating breast is distinctly different, on palpation, from those at pregnancy and puberty. The change in the breast after lactation produces various pictures to be seen on inspection and changes on palpation. A very common disease of the breast, *chronic cystic mastitis*, gives rise to the bilateral *lumpy* breast or *shotty* breast, or *dilated ducts beneath the nipple*, or to definite single and multiple tumors in one or both breasts.

Enlightened women now consult us for warts, moles; angiomas, of the skin of the breast, for subcutaneous fibromas and dermoids in the breast area, for the skin reaction after mosquito and other bites, for hypertrophy of the glands of the areola. In fact, my experience with benign lesions of the breast and in the region of the breast since my publication in 1921, eight years ago, has so increased that it is not only difficult to keep up with the study of the larger numbers of cases of the same type, but to correlate the new things.

The following stand out prominently and should be emphasized: (1) The increasing percentage of benign lesions for which operation is not indicated, but which must be recognized by inspection, palpation and the interpretation of facts in the history. (2) The difficulty of convincing women with pain in one or both breasts and no definite lump, that it is not a sign of cancer. (3) The greatest difficulty of distinguishing a definite from an indefinite lump, or

recognizing a definite lump in the lumpy breast, in the shotty breast, or one mixed with the palpable dilated ducts beneath the nipple. That is, a larger number of women every year are being referred to surgeons, because one or more members of the medical profession have thought they felt a definite lump, and that operation was indicated. This is not at all a dangerous mistake. In fact, it is fortunate for both, the women and the surgeons, providing the surgeon can distinguish between the definite and indefinite lump. If not, the woman is subjected to an unnecessary operation and may even lose the breast. But she does not die from cancer.

In the next group, which is fortunately smaller, the definite lump is looked upon as a "caked" breast or mastitis, and operation is deferred until the clinical picture of malignancy is distinct, and the chances of a cure very much reduced. Now, as a matter of fact, this area of mastitis is really like the caked breast of lactation mastitis. Even the women do not call it a "lump," but speak of it as an enlargement or a glandular mass, or even a caked breast. The one or more doctors who feel the breast never overlook finding the area on palpation, but because it feels so different from the majority of tumors or lumps in the breast and so much like the caked breast of lactation, it is diagnosed mastitis, because the majority of the medical profession today have not been taught, or have not learned from experience, that cancer of the breast may, in the onset, palpate like ordinary mastitis—tubercular, pyogenic or traumatic.

I will speak of mastitis or the caked breast again. It is a very dangerous thing to delay in this type of breast lesion.

A zone of mastitis in the upper and outer quadrant of the right breast was recently palpated by my associates Drs. Stewart and Cohn and me. To all of us it felt like cancer, but there were no malignant changes in nipple, skin or subcutaneous fat. On transillumination, it was darker than the surrounding breast, but a diffuse cloudiness, not a circumscribed, dark area, as pictured and described by Max Cutler of the Memorial Hospital in New York in his article on "Transillumination of the Breast" in *Surgery, Gynecology and Obstetrics*.

The next day, on the operating table, I thought I elicited fluctuation in this area, but I knew that edema around a buried cancer would give pseudofluctuation of this type. The only point in favor of chronic cystic mastitis was a somewhat similar, but much smaller and indefinite area in the upper and inner quadrant of the opposite breast. At exploration, it proved to be a thick-walled cyst buried in breast tissue in which there were other, smaller, cysts, and the surrounding breast tissue showed mastitis. The breast was saved. It could have been cancer, or tuberculosis. As the patient had never had children, we could exclude lactation mastitis.

To repeat, I will emphasize areas of mastitis again, hoping to influence clinicians not to delay operation in this group.

Benign Conditions of the Female Breast for Which Operation is not Indicated. Impressed by the fact that of the last 100 female patients who had come under my observation, more than one-half belonged to the group of benign lesions for which, we had learned, operation was not necessary, in December, 1921, I presented this new phase of the breast problem. In the introduction to this present paper I have recorded the fact that in these eight years the group had increased from 50 to 65 per cent.

My records in 1921 showed 267 cases which were divided as follows: (1) Pain; (2) painful scars; (3) discharge from the nipple; (4) retraction of the nipple; (5) lesions of the nipple suggesting Paget's disease; (6) history of disappearing tumor; (7) definite and indefinite single and multiple tumors in women under twenty-five years of age; (8) definite and indefinite single and multiple tumors in women over twenty-five years of age; (9) tumors in the axilla, aberrant breast, lipoma, lymph glands, lesions of the sebaceous and sweat glands; (10) unilateral hypertrophy; (11) diffuse *virginal* hypertrophy.

These groups have been studied and restudied frequently since. We know results in practically all the cases today. The incidence of cancer seems to be about the same as in any group of women of the same age who are followed for nine years.

I am unable to give the exact number of cases today—roughly, it is more than 1000. For example, shotty breasts have increased from 3 to almost 100. Judging from the letters and personal conversations I have had since this paper was published in 1922, it impressed my colleagues in internal medicine and general practice as very helpful.

In a paper by me on the "Clinical and Pathological Diagnosis of Diseases of the Female Breast,"² any remarks in regard to this group are conspicuous by their absence, so that it is appropriate for me to record in this journal the experience I have gained in these years. The benign conditions of the female breast for which operation is not necessary did not become prominent until the educational program had gone on for some years and until we had learned that operation was not indicated in many clinical manifestations of chronic cystic mastitis and in discharge from the nipple without a palpable tumor, or in discharge from the nipple with palpable dilated ducts beneath the nipple, or associated with a shotty or lumpy breast. As a matter of fact, this group did not begin to be prominent until about 1919.

1. *Pain.* We have educated women now to report when they experience pain, but do not feel a lump. Before this, they rarely, if ever, reported for pain only, and rarely for lump unless there was pain or rapid growth, or ulceration.

Again and again we have grouped benign and malignant tumors of the breast which had been operated upon as follows: Tumors,

no pain; tumor, interval, then pain; pain, interval, tumor; pain and tumor observed almost simultaneously. The interesting study is how frequently does pain in the breast antedate a malignant tumor, or how often is pain the symptom of onset in cancer of the breast? How frequently do women experience pain in the breast without the later development of cancer, even over a period of years? We can answer this with considerable exactness.

In 1920, we only had 50 patients who consulted us for pain only, and in whom we could find no definite tumor. There have been at least 200 more cases since then. Therefore, pain is a frequent observation in the breasts of women who apparently run no more risks of cancer or any other operable lesion of the breast than women who have no pain. In benign tumors, pain is a more frequent symptom of onset than in malignant tumors. I can explain this only by the fact that pain is more frequent in the breasts of the younger women within the age limits of the benign lesions, and less frequent in the breasts of women at the cancer age. The pain recorded in all these histories, in the *no operation* group, with the benign tumors and in cancer of the breast, shows the same variable character before the palpation of the lump. Pain after the knowledge of the lump by the woman is of no diagnostic value. It is important to remember that many women have pain in one or both breasts, most commonly experienced just before the menstrual periods. They may have localized pain in one breast for years; it may be associated with tenderness. The conclusion we reached in 1921 is still correct—pain and tenderness are of no value in the differential diagnosis of breast lesions. The value of pain is this—if it is a symptom of onset, it may lead the patient to feel a lump if present; if there is no lump it may bring the patient for an examination which should be repeated at short intervals for at least three months and then once a year. So far, I have never found a malignant tumor in a woman who sought examination for pain only. I have a record of only one case in which a malignant tumor of the breast was discovered during an ordinary physical examination, the patient being unaware of pain in the breast. We should continue to urge women to seek an examination the moment they feel pain.

Pain and Fear of Cancer. There is no question that the basic influence which brings the majority of women under medical observation with lesions of the breast, is the fear of cancer, and I trust that we can continue to be so fortunate as to keep this fear within limits, so that it will not put off the examination. When the examination reveals no lump to be operated upon, the most important thing to do—often a very difficult thing to accomplish—is to relieve the patient of fear. Repeated examinations and conversations will accomplish this.

2. *Painful Scar.* The statements of 1921 are still correct. Pain in a scar in the region of the breast is not a sign of recurrence of the

disease for which the operation was performed. The same factors which cause pain in the scar anywhere in the human body are active in scars in the region of the breast. I have never excised a scar of the breast for pain. When the patients are relieved of their fear of cancer, they put up with the pain in the scar. In recent years I have looked for foci of infection and removed them, if present, have advised frequent hot baths in cold weather, and extra flannel or woolen covering to prevent chilling of the scar area when the thermometer is low. Pain in the scar is largely a circulatory phenomenon. Add to this the fear of some serious disease, and the patient comes under the observation of the medical profession.

3. *Discharge from the Nipple.* I still hold to the opinion expressed in 1921 that discharge from the nipple, no matter what its character, is not a sign of cancer. We have made the same study of discharge from the nipple as we have made of pain, with practically the same conclusions. The number of cases we had observed to 1921 in which operation has not been performed, has now increased to more than 100. We have found that discharge from the nipple is observed in about 1 per cent of all groups of breast tumors—benign, malignant and “no operation.” This is about the incidence one would find of cancer. The causes of discharge from the nipple are, first and most frequently, a papilloma in a duct. Here the character of the discharge is hemorrhagic or serous. In galactoceles and in residual lactation hypertrophy it is like milk or cream. In dilated ducts beneath the nipple which may accompany chronic cystic mastitis, the discharge is not bloody nor serous. It is usually grumous and may be yellow, brown or green.

Discharge of blood from the nipple has been most frequently observed in a group of benign tumors called intracystic papilloma. The incidence of such discharge is recorded in about 50 per cent of the cases. It may be a symptom of onset and may be present years before the tumor is felt and removed. It may be observed simultaneously with the palpation of the tumor, or at intervals after the tumor has been felt. *We have not a single record of cancer of the breast developing in a papillomatous cyst*, unless the palpable tumor has been observed nine months or longer. I have no evidence that a woman who has a discharge from one or both nipples, and whose breasts, on palpation, are found free from tumors, runs any more risk of cancer than a woman who has pain and no palpable tumor, or any female who has neither. As Osler would say, the patient with pain in the breast, or discharge from the nipple should run less risk of cancer, because such symptoms should lead to more frequent examinations.

A small per cent—less than 10—of the patients who consulted the clinic for bloody or serous discharge from the nipple and at whose first and subsequent examinations no lump was felt, have developed

a lump months or years later, and this lump has been removed, and proved to be papillomatous cyst, and the breast has been saved.

In the majority of these patients ultimately, after years, the discharge ceases.

Today, for the first time, I operated upon a patient of mine who had observed a serous or bloody discharge from the right nipple at intervals over a period of nine years. She is now over fifty and has passed the menopause. At no examination had we been able to palpate a tumor. She has reported by letter at intervals of every six months during these nine years. She has been examined at least once a year by her family physician and less frequently at the clinic. The patient returned because, after an interval of about three years in which no discharge was seen, it has now reappeared and is bloody. There is no tumor to be felt. There is a small dark spot beneath the left discharging nipple, not seen beneath the right, on transillumination. The left discharging nipple is larger than the right, yet there is no keratosis, no signs of irritation suggesting beginning Paget's disease. As I have recently learned how to excise the nipple and a zone of breast beneath it in the benign stage of Paget's disease of the nipple, or for infected dilated ducts beneath the nipple simulating, clinically, early malignancy, I decided that this patient had better be relieved of the mentally annoying discharge, and malignancy absolutely excluded. Under procain, we removed the nipple with a small zone of skin including the areola, and a zone of breast beneath. As we cut through the breast tissue, we encountered no dilated ducts or cysts. Frozen sections from this breast tissue showed adenomatous areas and one small zone of papillary cystadenoma which is quite a common occurrence in a breast the seat of one or more papillomatous cysts within the ducts. After we had removed the mass and bisected it through the nipple, there was exposed a somewhat long, bottle-shaped, light-brownish mass, beginning 5 mm. beneath the nipple, about 8 mm. long, and 3 mm. in width. It had a distinct cyst wall and, on section, was filled with a grayish, friable papilloma. Sections showed a benign papilloma of the duct. There was no evidence of malignancy in any of the frozen sections. The patient was saved the mutilation of the removal of the breast.

During the same week another patient came under my observation with the recurrence of a discharge from the nipple after its first appearance seven years ago and after its last appearance two years ago. The question is, what are we to do for this group when the discharge persists for years, or recurs after years of quiescence? Will transillumination really help us in this group, as suggested by Max Cutler? Which is the best procedure—the excision of a zone of breast beneath the nipple, without the nipple, or with the nipple? I have performed both. It is a point to be settled by a restudy of this now very much larger group, but I can record here again that

no patient has, as yet, in our records, developed cancer of the breast, because we refused to explore the breast for discharge from the nipple.

4. *Retraction of the Nipple.* We have learned, since³ 1922, that intermittent retraction of one or both nipples is not a sign of malignancy, but of chronic cystic mastitis, usually of the Schimmelbusch type, or the shotty breast. I brought this out in 1921.⁴

It is well understood that retraction of the nipple of the congenital type, or of long duration, dating back to an old mastitis, is not a sign of cancer. But when one nipple has recently become retracted, whether a lump can be felt or not, cancer must be suspected, and, in my opinion, the breast should be explored. But this retraction may be due to chronic cystic mastitis. Retraction of the nipple of the malignant type has been observed now and then in every type of benign lesion of the breast, less frequently in encapsulated adenoma, a little more frequently in chronic cystic mastitis (3 per cent), much more frequently in lactation and tubercular mastitis, and, of course, most frequently in malignant disease of all types. The nearer the small palpable lump is to the nipple, the less reliance can be placed on retraction of the nipple as a sign of cancer. In demonstrating the presence or absence of retraction of the nipple, not only inspect, but move both arms up over the head and watch both nipples; pull the nipple forward, to see if one is more fixed than the other. The earlier we palpate a tumor of the breast after it is first felt by the patient, the more will we depend for diagnosis on exploration and frozen section, than upon retraction of the nipple, slight dimpling of the skin and atrophy of the subcutaneous fat. Regard, however, retraction of the nipple as a sign of malignancy, until there is positive proof that there is not cancer.

5. *Lesions of the Nipple Suggesting Paget's Disease.* In March, 1921, I had observed 3 cases of irritation of the nipple which healed under the treatment with cleansing, twice a day, with soap and water, using cotton and followed by medicated alcohol; then covering the affected nipple with vaselin and a piece of gauze fixed with adhesive straps. In 1924, I⁵ made a report on my entire experience with Paget's disease of the nipple. The 3 nonoperative cases had increased in three years to 7. The number now is more than 50. In 1924, 15 benign lesions of the nipple had been subjected to operation. In many the breast was unnecessarily sacrificed. Since the paper was written in 1924, and from the studies of the cases reported we now, when the simple treatment fails to heal the irritation of the nipple, excise it with the areola and a zone of breast beneath. If frozen sections reveal no evidence of malignancy, the breast is saved. If Paget's cancer is present, the complete operation for cancer is performed. Today we rarely see Paget's cancer of the nipple that can be diagnosed clinically. The majority of cases of irritation of the nipple heal under cleanliness and protection. There

is sufficient evidence to state that a neglected irritation of the nipple in a woman at the cancer age, has the same etiologic relation to cancer, as a neglected irritation of the nipple in a nursing mother has to an abscessed breast or lactation mastitis. Our studies show that prenatal care and the care of the nipple during the nursing of the child, have reduced mastitis abscess from more than 20 to less than 1 per cent. The educational program is bringing women with irritation of the nipple before the cancer stage. In every physical examination the nipples should be inspected for warts, keratosis and any form of irritation, and if these are present there should be immediate treatment. If this treatment fails in three weeks, the exploratory operation just described should be performed. I have no evidence that the congenital retracted nipple is more frequently affected with Paget's disease than the normal, but we have observed Paget's cancer in a congenitally retracted nipple. Therefore, it should receive the same inspection and the same treatment.

6. *History of Disappearing Tumor.* This is now established, with the exception of the caked breast and the lactation mastitis, which does not go on to suppuration, as a definite sign of chronic cystic mastitis. When patients observe any type of swelling or tumor or mass to vary in size, to entirely disappear, and then reappear in the same spot or in another area of the same breast, or in the opposite breast, we can safely conclude that the chances are that both breasts are involved in chronic cystic mastitis. But it does not exclude malignant disease, or other types of benign tumors. In all diseases of the breast other than chronic cystic mastitis the history of disappearing tumor has been recorded in 1 to 2 per cent of the cases; in chronic cystic mastitis in almost 20 per cent of the cases. When the palpable single tumor is the one that the patient has observed to show changes in size, or to have disappeared to reappear, this, of itself, suggests a benign cyst. If, in addition, the tumor is spherical, fluctuates and transilluminates clear, we have the almost certain diagnosis of a benign cyst. If, in addition, both breasts are lumpy, or shotty, or there are other, smaller similar tumors, the clinical picture of chronic cystic mastitis is established.

Tumor or Tumors in the Breast. Now that more and more women are presenting themselves for examination within a month of the first warning, we are palpating more and more frequently lumpy breasts, shotty breasts, dilated ducts beneath one or both nipples, multiple definite and indefinite tumors. That is, clinical manifestations of chronic cystic mastitis which is a disease like osteitis fibrosa of bone, in the majority of cases subside almost as quickly as they appear, so that after a few months' duration they are less and less frequently observed on palpation, although present microscopically.

There is another reason why, on palpation of the breast, we have to pay more attention to the entire breast and to both breasts.

This is due to the fact that when women have delayed months or years after feeling a lump, and the lump has not disappeared, the single lump is so definite that, with rare exceptions, the clinician occupies his full time in feeling this lump and recording its characteristics, and no attention is paid to the remainder of the breast and often there is no record of palpation of the other breast. During this period, as I have already stated, 80 per cent of the lumps were malignant and 50 per cent of these in the hopeless stage of cancer, while today the definite palpable, single lumps are about 35 per cent instead of 99 per cent, and one-half of them are benign.

Unless one had many opportunities to palpate the breasts of women in the earliest stage of all the lesions of the breast, one will not appreciate the difficulty of differentiation.

I have learned to divide breast tumors clinically into two great groups—those in which the patient is twenty-five years of age or younger, in which we need not think of malignant disease, and those in which the patient is twenty-five years of age or older, in which we must think of malignant disease.

For record in the history and on the index card, the letter (a) indicates a single definite tumor, (b) a definite tumor in both breasts, (c) two or more tumors in one breast, and (d) two or more tumors in both breasts. The letter (e) indicates a single indefinite area in one breast, (be, ce, de) designate multiple indefinite areas. Out of this classification there have arisen three definite types that may be composed of definite or indefinite lumps, or a combination of both—the shotty breast, the lumpy breast, and the dilated ducts beneath the nipple.

The first, most important new fact is the frequency, in the past few years, with which we may see a patient with a single lump difficult to class as definite or indefinite. If this single lump is the palpable area in either breast, it should be explored. The chances of its being malignant are almost 25 per cent, while the probabilities of malignancy in the perfectly definite lump are 50 per cent. As cancer may occur in the shotty breast, the lumpy breast, or in the area beneath the nipple in which there are dilated ducts, it is becoming more and more a triumph of tactile sensation to pick out the possible malignant tumor in these breasts filled with manifestations of chronic cystic mastitis.

We may state here that in the great majority of the cases in which the breast is the seat of a malignant tumor, there is no difficulty whatever to palpate it as a single mass. Cancer is very infrequent in the shotty breast or the lumpy breast, or when the ducts beneath the nipple are dilated.

7. *Tumor or Tumors in Woman Under the Age of Twenty-five.* It makes very little difference, if the patient is under twenty, whether the tumor is single or multiple, indefinite or definite, whether it involves one or both breasts, or is an area of mastitis

or is not. The nipple may be retracted or irritated, or there may be discharge from the nipple. Operation may be postponed, unless the tumor grows larger, or there are signs of an abscess. The indication for operation is to save the breast, and not to save the life of the patient. The most frequent tumor in women under the age of twenty-five years is an encapsulated adenoma which may be single or multiple.⁶ We must bear in mind that these encapsulated adenomas may be situated outside of the breast zone and may grow more rapidly than the breast at puberty, be diagnosed incorrectly as malignant, and the breast sacrificed when removing the tumor. Aberrant encapsulated fibroadenomas are not infrequently observed in young women. In former years when all females delayed after palpating a lump, we frequently observed large tumors of the breast. The majority were sarcomas which had developed in a neglected intracanalicular myxoma.

The possibility of an aberrant adenoma growing rapidly and of the intracanalicular myxoma becoming sarcoma after a certain enlargement, is the chief reason for removal of a tumor near, or in, the breast of any female under twenty years of age, when there is any sign of growth. After the age of twenty, all palpable tumors in, or near, the breast should be removed. Left alone, they may complicate pregnancy or lactation, or later in life develop into cancer, and—very interesting to record here—these little tumors of ten years' duration or longer which are now being excised by surgeons simply because the woman has just learned that it is dangerous to leave a lump alone, are being diagnosed by pathologists as cancer. Two such cases have recently been referred to me.

These old encapsulated adenomas of any type become very fibrous and, in some instances, may even calcify; the basement membrane beneath the epithelial cells of the old parenchyma is frequently absent; masses of old epithelial cells in solid clumps, or papillomatous masses are surrounded by fibrous stroma—the gross histologic picture of cancer, but the individual epithelial cells are not, morphologically, cancer cells. It is, therefore, safer to have these little encapsulated adenomas removed before the young female passes into the cancer age and before circulatory changes obscure the microscopic picture. I have called attention before to the frequency with which all types of encapsulated adenomas have been diagnosed, by a certain number of pathologists, cancer, but I have never before called attention to this new danger of leaving a quiescent lump in the breast of a young woman alone for the fear that later in life it may be removed and diagnosed cancer, and the breast sacrificed.

All obstetricians are familiar with the enlargement of both breasts in the newborn child and the copious discharge from the nipple. The etiologic factors are unknown. It apparently has no relation to diseases of the breast later in life. If the breasts are kept scrupulously

clean and infection avoided, these breasts never give trouble. Tumors in and about the breasts of children are rare. If they are not directly in the breast, it is, on the whole, safer to remove them, even when they do not exhibit growth, because sarcoma is very common in the young.

At puberty, unilateral hypertrophy of one breast is not rare. There should be no difficulty in excluding tumor, unless the breast gets very large, when one should suspect a central adenoma which can be found and removed by exploration, and the breast saved. As a rule, very quickly, the other breast develops and catches up. Diffuse virginal hypertrophy is a bilateral disease. Its cause is unknown. We know of no way of arresting it. It is my rule, when this hypertrophy reaches a certain size, to perform a plastic operation, removing one or more wedge-shaped segments. I had only one opportunity to practise it—it was successful. Lesser degrees of diffuse virginal hypertrophy are getting more and more common in this "no operation" group. This type of breast, in its diseases, does not differ from the normal breast, but in its function, it differs distinctly. Often there is no milk, or, if any, it is scanty. It is one of the rarest occurrences in this country to see a diffuse virginal hypertrophy reach the size recorded by G. B. Johnson⁷ of Richmond, Virginia, in 1903.

8. *Tumor or Tumors in Women Over the Age of Twenty-five. Shotty Breast.* I⁸ described the clinical and pathologic picture of 13 such cases among 350 examples of chronic cystic mastitis, and called it diffuse nonencapsulated cystic adenoma, or papillary cystadenoma. It was first described by Schimmelbusch and Réclus in 1906, I⁹ employed the term senile parenchymatous hypertrophy. The 13 cases described in 1921 were all operated upon, either the complete operation for cancer, or the removal of one or both breasts was done, in order to protect the patient from cancer. The earlier cases subjected to the complete operation for cancer were diagnosed adenocarcinoma in diffuse papillary cystadenoma; the later cases were called benign papillary cystadenoma. Within a year, I¹⁰ employed the term "shotty" breast and described 6 cases in which operation was not performed; the earliest in April, 1921.

Since then we have records of more than 100 cases, not subjected to operation, which have been followed, and in these breasts cancer has not developed. The longest observation is eight years. During the same period 34 patients have been subjected to operation, either partial removal of a zone of the breast, or of the entire breast, or the cancer operation, but all were finally diagnosed as microscopically benign. In 3 instances, a palpable nodule distinct in a shotty breast had been explored, recognized as cancer in the frozen section, and the patients subjected to the complete operation. Shotty breasts, therefore, are now a common clinical finding. With the rarest exceptions, operation is not indicated. In a few there must

be exploration for frozen sections to ascertain if malignancy is present in an area or a tumor which can be palpated distinctly in a shotty breast. A paper on this form of chronic cystic mastitis will be soon published in detail.¹¹

There is nothing distinctive on inspection. There may be a little discharge of grumous material from the nipple. The shotty breasts are practically always bilateral, although the degree may be more marked in one breast. These patients have rarely much subcutaneous fat, the majority are underweight. The breasts are rarely large. We never observe the shotty breast, the diffuse nonencapsulated papillary cystadenoma in large fatty breasts. Either the breasts have never lactated, or it is some years since the last lactation. It is practically never seen after the menopause. When one palpates the upper and outer quadrants of both breasts, one will think at once of the breasts at puberty or pregnancy. The parenchyma is distinct, and as a rule it is filled with minute shotty masses. The further development is a distinct edge like the edge of the liver, and, still further, the breast can be lifted up, like a saucer, and it then assumes its shape. This condition may involve a quadrant, a hemisphere, or the entire breast. Often one or both breasts are painful or tender, and this pain and tenderness are most marked just previous to the menstrual period.

Not infrequently one can palpate one or more larger tumors or masses in one or both breasts, which as a rule feel like minute cysts. We have only practised transillumination the past six months. The shotty breast is not as translucent as the fatty senile breast, but there were no dark areas in those that we have transilluminated up to date. The cases that have been subjected to operation, have been those in which we could palpate a single tumor that suggested the possibility of malignancy, or because the breast felt more indurated or less shotty.

There is not so much difficulty, on palpation, in picking out the group among the shotty breasts that should be explored, but there will be great difficulty in interpreting the microscopic frozen section, unless one is familiar with the various histologic changes in chronic cystic mastitis. I have pictured them in the *Archives of Surgery* for November, 1921, in Figs. 32 to 91. These pictures are just as good today as when published and practically no new pictures have been encountered. I recommend to pathologists in the operating room the study of these pictures, and I suggest to clinicians, when they have this type of case subjected to operation, to have this volume of the *Archives* present for reference.

Dilated Ducts Beneath the Nipple. We have been slow in recognizing this variety of chronic cystic mastitis as a definite clinical entity. In 1921,³ I had 22 cases; in 1923¹² I was able to report seven examples of the so-called varicocele tumor of the breast which had been observed since 1921. There have been at least 60 cases since

then that have not been operated upon. As a rule, women with dilated ducts beneath the nipple are older than the group of women with shotty breasts, they are approaching the menopause. They are apt to be overweight, while the patients whose breasts are the seat of diffuse papillary cystadenoma are underweight. The condition is usually bilateral, if carefully examined. The patient's attention to the breast is attracted more frequently by pain and tenderness than by a lump, and least frequently by discharge of thick, grumous material from the nipple. On palpation, one feels

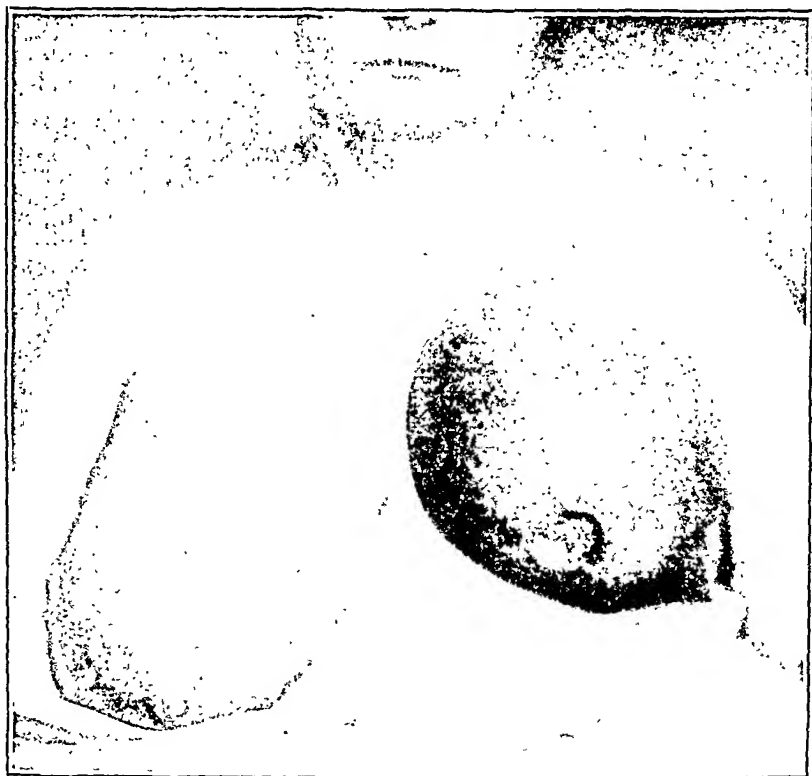


FIG. 1.—Hopeless cancer of the left breast. Patient absolutely ignorant of her condition; has no fear or discomfort. Came to the clinic because of cough and bloody expectoration. The patient lives in a locality in the country where few, if any, messages from the outside world are received or read. This is the type of cancer described by Billroth, Velpeau and Paget.

beneath the nipple and areolar zone one or more masses, usually in the shape of worms and often not larger than the largest angle worm. Each dilated duct palpates distinctly, because there is very little subcutaneous fat here. Usually the palpable tumor is not tender. Now and then pressure on the dilated duct brings forth pastille material from one or more ducts. Once felt, it cannot be mistaken in this stage, and for this stage there is no indication for operation. But the duct may become infected. If the infection is acute there will be a rapid development of a typical abscess which can be opened and drained like any other abscess. But more fre-

quently the infection is chronic, and the inflammatory reaction around the duct palpates like a possible malignant tumor, and the nipple may be slightly fixed and retracted. It is my rule to explore such cases and decide from the gross and frozen-section appearance whether it is malignant. There should not be much difficulty, as shown in the illustrations reproduced in the *Archives of Surgery*.

Dilatation of the ducts beneath the nipple may be present in any breast of a woman approaching menopause or later in life. When we look over the gross notes on cancer of the breast, we find dilatation of the ducts distinctly more frequent than cysts, or the Schimmelbusch type of chronic cystic mastitis. But I have not a single instance of a definite cancer beneath the nipple surrounded by dilated ducts. Cancer situated in the nipple and areolar zone is relatively infrequent.

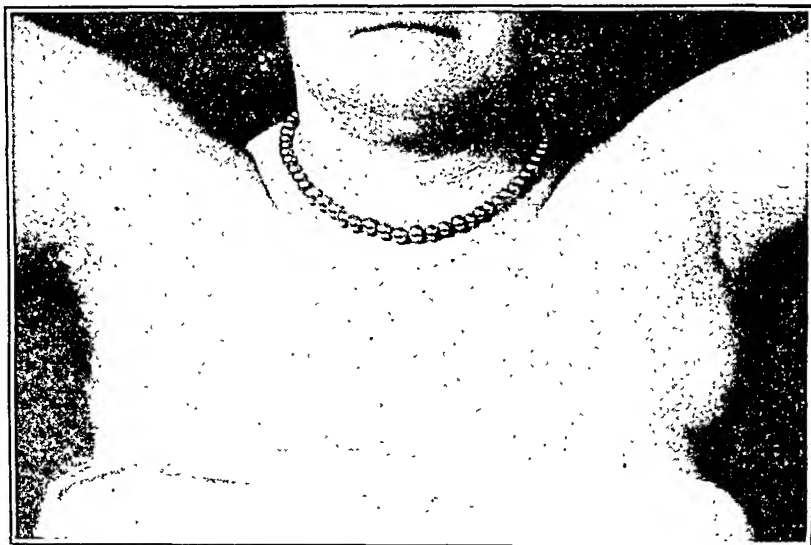


FIG. 2.—Photograph of an enlightened woman who has recently observed a lump in the left axilla. It was diagnosed aberrant breast tissue. Operation was not performed. There has been no trouble during a period of four years since. Enlightened women in this group have only 17 per cent chances that their lesion is cancer, and, if cancer, 60 per cent chances of a cure.

With this clinical knowledge, one should be able to recognize tumors beneath the nipple of the dilated-duct type, and save most patients from operation. But when infection has changed the clinical appearance, one must differentiate by excising the zone of breast beneath the nipple, in some cases with the nipple, as already described for Paget's disease, and decide as to the presence or absence of malignancy. Remember that the gross findings of dilated ducts filled with grumous material is against cancer, also that the frozen section may be difficult to interpret, because the periductal lymphoid granulation tissue will destroy the basement membrane and basal cells of the duct and the rapidly proliferating epithelial cells

of the duct will be found growing in this granulation tissue, simulating cancer. See Fig. 6, page 509, in the *Archives of Surgery* (*loc. cit.*).

Lumpy Breast. Warren, of Boston, described them as "cobblestone" breasts, and the Warren incision was devised in order to expose even a hemisphere of the breast and to remove by posterior excision one or more of the palpable masses which as a rule are not cysts. Sir G. Lenthal Cheatle, of London, in his excellent contributions to chronic cystic mastitis, has called attention to these lumpy breasts. In 1921, in 350 cases of chronic cystic mastitis, I found that there were 76 examples of this type, and most of these patients had lost one or both breasts, or had been subjected to the complete

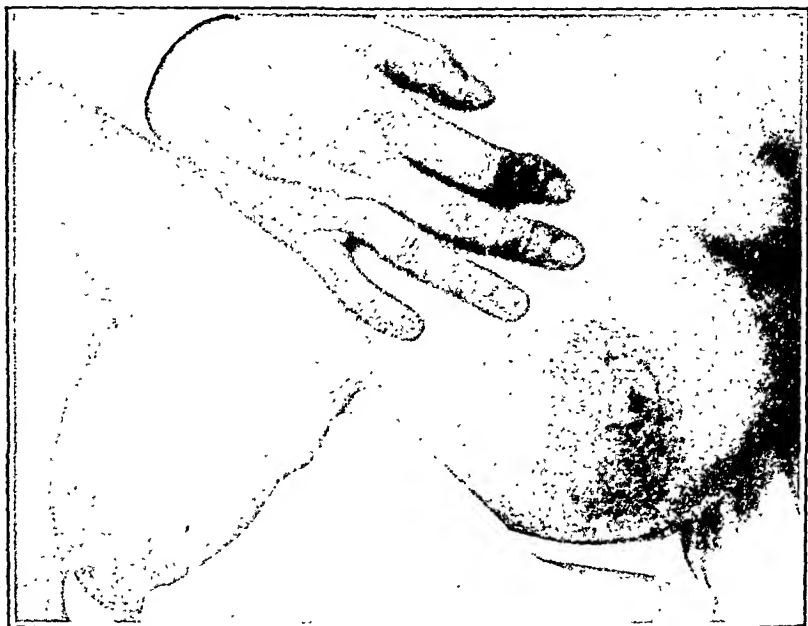


FIG. 3.—Paget's disease of the nipple in the stage of superficial ulceration. In this case excision of the nipple, frozen sections showed cancer, and the complete operation for cancer was done.

operation for cancer. Since then I have never operated in cases of this kind unless there was a single tumor either distinctly palpable, or sufficiently different to justify exploration and frozen sections. In the past eight years I have records of at least 200 cases not operated on, but I find that in the laboratory 87 examples have been referred there for diagnosis. In many, the exploration had been unnecessary, and in every instance the removal of one or both breasts was not indicated by either the clinical or pathologic picture. When 35 per cent of women who seek the advice of a clinic after a warning of trouble with the breast have definite tumors, on palpation, and 65 have not, bilateral lumpy breasts are by far the most common finding. Yet my laboratory records now 163 speci-

mens of this condition received from different sources. In not more than 40 of these was exploration justifiable.

The majority of lumpy breasts are due to chronic cystic mastitis scattered in areas throughout the breast. These areas are not unlike areas of nonencapsulated adenoma, and, microscopically, they may resemble fibroadenoma, cystic adenoma and—rarely—intracanalicular fibroadenoma. In a number of instances the nodules are due to one or more minute cysts or dilated ducts. With the rarest exceptions, the multiple cysts, like the single cyst, palpate like definite tumors. Multiple lipomas may produce a lumpy breast. Sometimes the senile breast is distinctly lumpy due to irregularities in the distribution of fat and fibrous breast stroma. The lactating breast may be lumpy, and for some years after the last lactation, the breast may remain lumpy. In some instances, these lumps are due to residual areas of lactation hypertrophy. I have found such areas fourteen years after the last lactation.

In a few instances, when the upper and outer quadrant of the breast is shotty, the lower hemisphere is lumpy. Distinct cysts palpating like single or multiple tumors are more frequently found in lumpy breasts than in shotty breasts. Distinct dilated ducts beneath one or both nipples are found in shotty breasts only rarely, but frequently in the lumpy breast. Single and multiple cysts often accompany dilated ducts beneath the nipple.

In brief, all the clinical pictures, on palpation of one or both breasts, are associated with definite pathologic changes, and the most common factor in these is chronic cystic mastitis.

No one can diagnose breast lesions safely today without familiarity with the clinical and pathologic pictures of chronic cystic mastitis.

Multiple Definite Lumps in One or Both Breasts. In younger women the most common finding is encapsulated adenoma; in older women some pathologic variety or stage of chronic cystic mastitis. Rarely is cancer found when the breast is the seat of multiple areas of chronic cystic mastitis or adenoma. Rarely is cancer a multiple tumor in one breast, and when such is observed, the other malignant areas are metastatic. Very rarely does cancer appear simultaneously in both breasts. As a rule benign multiple lesions are bilateral, malignant unilateral. Too many breasts of older women are sacrificed because of multiple blue-domed cysts, which is a perfectly distinct clinical picture. I reported 28 cases in 1921, and find 14 more in 1929, a total of 42 cases.

Areas of Mastitis or Caked Breast. My associate, Dr. L. Clarence Cohn, has been going over this subject for some years, and his paper is almost ready for publication. In the *Boston Medical and Surgical Journal* (*loc. cit.*) I presented, with illustrations, diffuse mastitis, lactation mastitis, tubercular mastitis, nonlactation mastitis, comedo-adenocarcinoma diffusely involving the breast with the clinical picture of mastitis, and carcinoma mastitis. I have already dis-

cussed this clinical picture and described a recent case in which a zone, almost a hemisphere of the breast, was the seat of a mass which palpated like mastitis. At exploration, it was due to multiple cysts buried in breast tissue. So we must add to the types described in 1922 the fact that chronic cystic mastitis of the cystic variety may produce a tumor of the diffuse mastitis type. We have already emphasized that the shotty breast simulates mastitis, but has, in addition, multiple shotlike areas and may develop a saucer-shaped palpable mass. Recently, I operated on a woman with cancer mastitis that had reported to her medical adviser the moment she felt the indefinite lump in her breast, and this patient has been under observation and treatment for six months with the diagnosis of mastitis. She had been treated with sunlight and violet rays. As the mass became larger and the nipple fixed, suspicion of malignancy urged them to refer the patient to a surgeon.

There is nothing more insidious than the type of cancer that produces an area of induration like a caked breast. There are really only two types of mastitis in which delay is justifiable—one, the pregnant or lactating breast with fever and leukocytosis and clinical evidence of inflammation. The other is the typical shotty breast, which is bilateral. But when the shotty breast presents a diffuse, hard zone, without the multiple shotlike areas, one must explore. As I am writing this for clinicians and not surgeons or pathologists, I believe I will accomplish better results by saying no more, except—
Do not delay when the mass in the breast of a woman over twenty-five suggests mastitis on palpation.

9. *Aberrant Breast Tissue in the Axilla.* In 1921, I had notes on 17 cases—14 unilateral, 3 bilateral. The number now has increased to about 50 cases. Cancer in breast tissue in the axilla has occurred in about 3 per cent of the cases. The patient's attention to aberrant breast in the axilla is attracted by seeing or feeling a mass there which is quite prominent on inspection, and palpates like breast tissue. Now and then this mass proves to be entirely composed of fat. So far I have never observed chronic cystic mastitis in aberrant breast tissue, although this tissue does enlarge during pregnancy and lactation. In none of my cases have there been nipples in these axillary masses of breast tissue. Operation is not indicated, unless one can palpate a definite tumor, or unless the mass gets large enough to justify its removal.

Sebaceous and Sweat-gland Nodules in the Axilla. Their chief interest has been in patients upon whom the complete operation for cancer has been performed, months or a few years previous to the appearance of these single or multiple nodules in the hair zone of the axilla. In all of the cases of which I have records, the diagnosis of recurrence has been made, and many of the patients were subjected to irradiation. These tumors are, clinically, definitely inflammatory. Excision and frozen section will confirm the diagnosis. It is unnecessary to remove them to accomplish a cure.

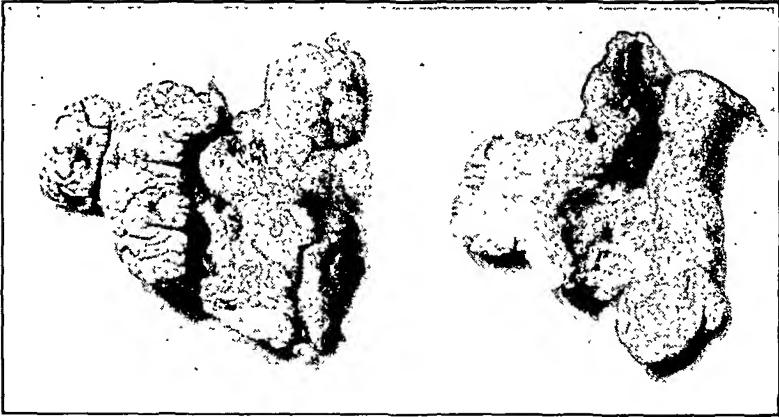


FIG. 4.—The excised nipple in an earlier stage than in Fig. 3. The frozen sections showed cancer. Complete operation was performed.



FIG. 5.—Pathol. No. 25560. Photograph of a typical blue-domed cyst buried in senile fatty breast.

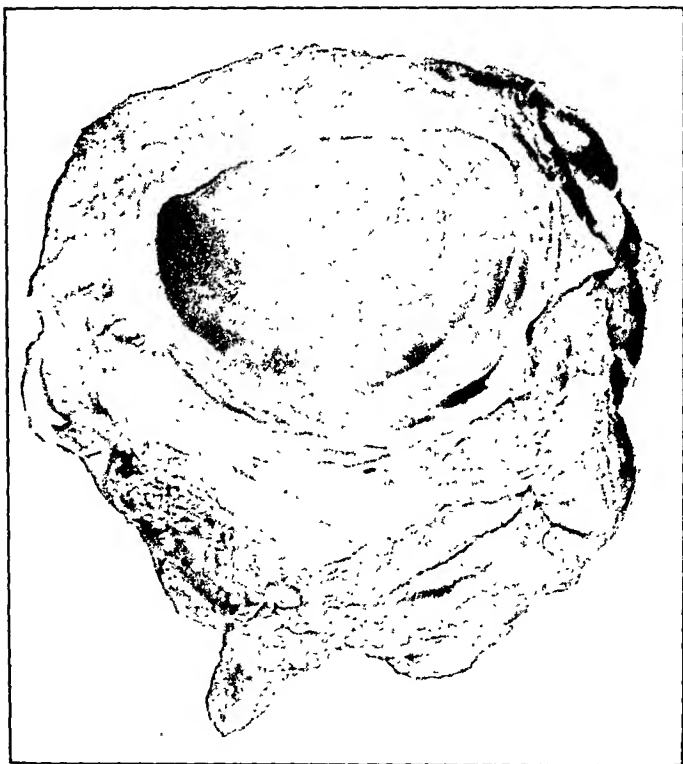


FIG. 6.—Pathol. No. 10940. Photograph of a bisected blue-domed cyst removed with a zone of breast tissue. Note the thin, smooth wall of the cyst. The surrounding breast is a mixture of fat, elevated gray dots of adenomatous areas, and one minute cyst.



FIG. 7.—Pathol. No. 37068. Photograph of an encapsulated adenoma. Surrounding breast is adenomatous. This adenoma proved to be a solid intracystic papillary adenoma.

10. *Unilateral Hypertrophy at Puberty.* I have already referred to this; unilateral hypertrophy at later ages, with the rarest exceptions, means some form of encapsulated adenoma, and if the mass is larger than a quadrant, beware of sarcoma.

It is interesting to note that in the male the diffuse hypertrophy begins in one breast; in from three to six months later it appears in the other breast, and, if left alone, will disappear in a few months. Cancer of the breast in the male is insidious, and fully developed clinically it is usually hopeless. For this reason, when a man comes under observation with an enlargement of one breast of a few weeks' duration, it is best to excise the whole area with the pectoral fascia under local anesthesia and exclude malignancy by frozen sections. If the lesion is benign, you should prepare the patient and his physician for the subsequent enlargement of the other breast which may be left alone.

11. *Diffuse Virginal Hypertrophy.* This has been discussed, and there is nothing to add, except one very remarkable pathologic finding which demonstrates that benign pathologic processes may resemble closely malignant ones.

Through the courtesy of Dr. Johnson (*loc. cit.*) I was able to study the lesions of his case. On cross-section through the huge breast (Fig. 4) the hypertrophied breast tissue had destroyed all the subcutaneous fat by pressure or infiltration, and lobules of breast parenchyma were found directly beneath the corium.

New Benign Lesions of the Breast for Which Operation is not Indicated. I find that since my article in 1921, a number of patients have come under observation and have been placed in this "no operation" group whose lesions cannot be classified under the 11 headings just discussed.

12. *Changes in the Breast the Result of Atrophy After Lactation.* When the patient is in the proper position for inspection and palpation, that is reclining on her back with her arms over her head, one may observe that the nipples fall into a depression in the breast which can be palpated almost like a crater, and the areola and skin around the nipple are thrown into wrinkles. This is usually present in women who have nursed one or more children and the condition may persist throughout life. It is not a sign of cancer. It usually disappears when the woman sits up or places the arms to her side when she is lying down.¹³

It is important to bear these changes in mind, because this picture of the nipple and skin might suggest malignancy.

13. *Skin Lesions of the Areola and Skin Over the Breast.* These should be treated just the same as skin lesions elsewhere in the body. Elevated pigmented moles and warts should be removed. But every now and then one may feel in the skin of the breast a nodule, not unlike the skin metastasis from a cancer of the breast. In a very few instances a skin metastatic nodule may be the first sign of cancer

of the breast. The microscopic study of such a nodule after removal, will differentiate it.

The little skin dermoids always have a pucker or dimple on top and if they were buried in the breast, would suggest malignancy. On the whole, it is safer to remove them. There have been a number of cases of insect bites which produce a skin nodule similar to that following the injection of fluid into the skin. There may be a red area around it. Now and then erysipelas develops. Less frequently beneath it, an inflammatory reaction takes place giving rise to a tumor or mass which palpates like malignancy or mastitis.

The Proper Position for Examination of the Breast. Since my description of this, with illustrations, in 1921, there are only two new statements. The most important is the transillumination, as described by Max Cutler.¹⁴ This additional aid has been employed in my clinic in every case for a number of months. In the roentgenological department of the Medical School in Rochester (N. Y.) they are making Roentgen ray plates of the breast, trying to picture the soft part lesion, as they would a lesion of bone. Transillumination is quicker, but the Roentgen ray leaves a more accurate record. I would advise against depending upon these procedures until one has gained considerable verified experience.

The patient should be stripped to the waist and so prepared that the abdomen can be palpated. She should recline on a couch or examining table, on her back, chest and head slightly elevated. The fingers of both hands should interlock over the head. The examiner should not know which breast is involved until inspection, palpation, and transillumination are completed. On inspection, first look carefully at the nipples. Any keratosis or irritation of the nipple should receive immediate attention, and the patient then and there instructed how to treat it. Do not touch the nipple or areolar area until the last. Look for axillary masses and the thyroid area. Note the changes which you can see in the nipple and the skin around it. On palpating use both hands first, feeling similar areas of both breasts at the same time. Use your fingers as you would when playing the piano. Do not grasp the breast tissue and pick it up—it will give you a wrong impression. Pass the fingers of the hand a number of times around the periphery of the breast and into the axilla, and palpate as you would playing the piano. At once you can distinguish the shotty breast and the lumpy breast. At once you can tell whether there is an edge to the area of involved breast. Then you can lift up the edge and see if it is saucer-shaped. Now palpate the mid zone in the same way. At any moment you may feel one or more definite tumors. Leave them alone temporarily and go on with your examination of both breasts. Now palpate the areolar area for dilated ducts. As a rule this may induce an apparently retracted nipple to become prominent. The last thing to do is to pull on the nipple to see if it is fixed. Now make a diagram of both breasts and record the position

of definitely palpable lumps by circles showing their size and position. Write the word "shotty" or "lumpy" in the area in which you have found these conditions, and the words "edge" and "saucer" if this is brought out by palpation. Write the letters (dd) near the nipple if you find dilated ducts. Now move the arms from their elevated position down to the sides of the body, one or both, and note whether one breast or nipple is more influenced by this motion of the arms than the other. Recent experience has convinced me that we must not put too much reliance on differences brought out by this maneuver, unless it is very marked it is of no value. Now palpate the single lump, get its movability, does it fluctuate; does the skin over it dimple when it is pushed forward; is the subcutaneous fat between the tumor and the skin atrophied; what does the tumor feel like; is it spherical like a cyst, lobular like an adenoma, infiltrating like cancer, or is it an area of mastitis? How does the breast palpate around the lump? Are there other definite lumps?

Then ask the patient what she has felt. All doubtful cases should be examined again the next day, and some cases should have repeated examinations within the next few months if it is decided that operation is not indicated.

Shall we postpone operation if there is a single definite tumor in one breast which palpates like a spherical cyst and fluctuates, and transilluminates clear, and when this and the other breast are otherwise normal? I am beginning to do this in a few instances. Unless you have had considerable experience this postponing the operation may be dangerous. However, if, in addition, there is a definite history of change in size or even disappearance, and both breasts are lumpy, delay is less dangerous. If there are definite multiple tumors, there is no danger in delay.

In all other types of a definite single tumor in women over twenty-five years of age, any delay is unjustifiable, and there is no way, clinically, of distinguishing the benign from the malignant. It is also safer that such a patient should be operated on in a hospital where the surgeon is prepared to make and interpret frozen sections during the operation.

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SECONDARY ANEMIA IN PREGNANCY AND IN PUERPERIUM.

A STUDY OF THREE HUNDRED PATIENTS.

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THE exact nature and course of secondary anemia affecting the gravid woman is not well understood. For this reason, the present study of the subject of anemia in pregnancy and in puerperium has been undertaken.

Blood examinations, made in 300 women in the various periods of gestation and in the puerperium, form the basis of this communication. A special effort was made to determine, if possible, the relationship of the existing anemia to the various associated maternal conditions.

An analysis of the red blood cell counts and hemoglobin determinations in 200 dispensary maternity patients and 100 private patients is presented in the accompanying tables and figures.

Routine hematologic examinations have been made in all patients registering at the prenatal clinic since March, 1928, the examinations consisting of erythrocyte and leukocyte counts, differential counts, hemoglobin estimations, Wassermann tests, and blood sedimentation tests.

The first count was made at registration of the patient, the second within forty-eight hours of delivery, and a third count five to eight days later. Additional counts were performed at term in a number of ward patients. The examinations of the private patients were made a few days to a few hours before delivery.

The ward patients were chiefly of the poorer classes, and were more or less undernourished. None of the patients studied suffered from any acute infectious disease or from any complication with hemorrhage during pregnancy.

All the blood examinations were made by one qualified technician who devoted his entire time to this work. The Thoma hemacytometer, with the Leitz counting chamber supplied with the Neubauer

ruling, was used for cell counting. The percentage of hemoglobin was determined with the Dare hemoglobinometer. This instrument was selected, because it is easily read and sufficiently accurate for the purpose of this study. In this method 13.8 gm. of hemoglobin per 100 cc. of blood is regarded as 100 per cent. In 100 women between the ages of eighteen and thirty years, Osgood and Haskins⁴⁰ found the average hemoglobin content to be 13.69 gm. per 100 cc. of blood, practically the same figures as those on which the Dare instrument is based.

Historical Review.—Anemia complicating pregnancy has been the subject of numerous investigations since Nasse,^{38,39} in 1836, first stated that the number of red blood cells was reduced in the pregnant woman and spoke of the “anæmisierenden” influence of pregnancy. Much better known than the secondary or so-called physiologic anemia of pregnancy which is the chief consideration of this paper are: (1) The pernicious type described by Channing¹² in 1842, and, (2) the severe form of hemolytic anemia reported by Rowland,⁴⁵ Murdock,³⁷ Allan³ and others. A marked divergence of opinion exists concerning the nature of the mild form of secondary anemia frequently observed in pregnancy.

Among the authors who found that the erythrocyte and hemoglobin contents were unaltered throughout pregnancy, or only slightly diminished, may be mentioned Spiegelberg and Gescheildlen,⁵¹ Wild,⁵⁴ Adachi,¹ Terhola,⁵² Limbeck³³ and Engelsen.¹⁷ More surprising is the work of Schroeder,⁴⁸ Carton¹⁰ and Zangemeister,⁵⁶ who found an actual increase in the number of red blood cells.

That a definite anemia does exist in pregnancy was, however, shown by Fouassier,¹⁹ in 1876, Kosina and Ekert,³⁰ in 1883, Meyer,³⁵ in 1887, Dubner,¹⁶ in 1890, Henderson,²⁴ in 1902, Bar and Daunay,⁶ in 1904, and Blumenthal,⁹ in 1907.

Ingerslev²⁷ in 1879, found an average of 5.59 million red cells per c.mm. of blood in 10 nonpregnant women, and an average of 5.43 million red cells in 40 women at term. He concluded that a hydremic condition was not present, and that any difference in the counts before and during pregnancy must be due to the general health of the woman.

Thompson⁵³ found a high erythrocyte count at the beginning and end of pregnancy, and a low count in the interim. He noted an average hemoglobin percentage of 67.5 in the second month of pregnancy, 65 in the fourth month and 85 during the ninth month. Given²¹ observed an anemia in women at term, increasing in severity shortly after labor, though the count, he claimed, would return to normal during the puerperium. Sondern⁵⁰ found a reduction of from 500,000 to 750,000 red blood cells per c.mm., and a 10 to 15 per cent drop in the hemoglobin content, during the first half of pregnancy. Dietrich¹⁵ made blood examinations every fourteen

days over a period of three months antepartum, and found that a definite anemia was present.

Osler⁴¹ reported a case of severe anemia in a primigravida who was well before the time of conception. The anemia was recognized in the sixth month of pregnancy. The blood examination gave 864,000 red cells per c.mm., and 20 per cent hemoglobin; also relative lymphocytosis and anisocytosis and presence of normoblasts. Spontaneous labor occurred at the end of the seventh month. The patient was reported to be perfectly well two years later.

Gram²² records the examination of 59 pregnant women with an average of 71 per cent of hemoglobin for the first trimester, 72 per cent for the second, and 79 per cent for the third. There was also a reduction in the volumes per cent from 40 to 37. This is equivalent to a 7 to 10 per cent reduction in hemoglobin content. Adler² in studying 11 cases of anemia in pregnancy, found an average hemoglobin of 50 per cent and an average erythrocyte count of 3,680,000. He also observed rapid recovery to occur in the puerperium.

Larrabee³² reported a series of 17 cases of severe anemia in pregnancy and puerperium, 8 of which were pernicious in type. He stated that the blood picture of pregnancy may be that of a secondary, pernicious, aplastic, or atypical form of anemia.

Kerwin and Collins²⁸ reported hemoglobin contents as low as 55 per cent. They analyzed 30 cases in the first trimester, finding an average of 83 per cent hemoglobin; 88 cases in the second trimester averaged 83 per cent, and 86 cases in the third trimester averaged 82 per cent. Balfour⁵ studied 150 women with severe anemia at the Bombay Clinic in India. The anemia here occurred during the sixth and seventh months of pregnancy, in many cases associated with fever and diarrhea. Lyon³⁴ observed that 38 per cent of the women examined in the last trimester of pregnancy showed a hemoglobin percentage of 70 or less. Davis¹⁴ cited 2 cases of anemia in pregnancy with a hemoglobin content below 50 per cent. Two weeks after delivery the percentage was normal. Galloway²⁰ found that anemia existed in all of the three trimesters of pregnancy. In the first twelve weeks of pregnancy, 87 patients gave an average hemoglobin of 72 per cent, and an average red cell count of 3.63 million. Between the twelfth and twenty-eighth week, 84 hemoglobin determinations in 77 patients rendered an average of 70 per cent, while the average of 66 erythrocyte counts was 3.56 million. Between the twenty-eighth week and term, the average of 72 hemoglobin estimations in 69 patients was 71 per cent. Forty-one erythrocyte counts, made after the seventh month, gave an average of 3.82 million.

The recent reports on the blood determinations in normal women, published by Osgood⁴⁰ and Haden,²³ have provided standards with which our results may be satisfactorily compared. Haden found an

average of 4.26 million red cells for a group of 12 normal women of all ages. Osgood reports an average of 4.8 million cells, based upon the examinations of 100 normal women between the ages of eighteen and thirty years. For the purposes of the present study the normal low limit has been set at 4 million, all patients with counts below this figure having been considered as anemic.

Results of Blood Examinations.—Table I shows that 21 (10.5 per cent) of the 200 counts in ward patients were taken in the first two trimesters, 156 (78 per cent) in the third trimester, and 23 (11.5 per cent) during labor. For simplicity of presentation, these counts have been divided into five groups. Group 1 comprises the counts of 4 million or over, and patients with this count have been considered as normal. Group 2 includes counts of 3.5 to 3.99 million cells per c.mm. (mild anemia); Group 3 comprises counts of 3 to 3.49 million cells (moderate anemia); Group 4 includes counts of 2.5 to 2.99 million cells (severe anemia); and Group 5 comprises all counts below 2.5 million (very severe anemia).

TABLE I.—RED BLOOD CELL COUNTS ARRANGED ACCORDING TO TIME OF PERFORMANCE OF TEST.

Period in pregnancy.	Number of cases.	Millions of red blood cells per c.mm.					Total number of counts below 3.5 millions.
		4.0 or over.	3.5 to 3.99.	3.0 to 3.49.	2.5 to 2.99.	2.0 to 2.49.	
Up to and including sixth month . . .	21	6	8	7	0	0	7 (33.3%)
From seventh month to onset of labor . .	156	17	52	61	21	5	87 (55.7%)
During labor . . .	23	7	10	2	4	0	6 (26.0%)
Total	200	30	70	70	25	5	100 (50.0%)

Showing that red blood cell counts below 3,500,000 per c.mm. were given by 33.3 per cent of the cases in the first two trimesters of pregnancy, 55.7 per cent in the third trimester and 26 per cent during labor.

Table I also shows that 7 or (33 per cent) of the 21 patients examined in the first two trimesters of pregnancy had a moderate anemia. Of the 156 women who were examined in the third trimester of pregnancy, 87 (55.7 per cent) had an anemia varying from a moderate to a very severe grade, while only 6 (26 per cent) of the 23 patients examined during labor had red cell counts below 3.5 million. It was also noted that 100 women, one-half of the entire group of 200 examined, gave cell counts of 3.5 million or less.

For the purpose of this study, 75 per cent hemoglobin was arbitrarily chosen as the border-line below which the patient was considered to have a low hemoglobin content. Table II indicates that

163 ward patients (81.5 per cent of the 200) had less than 75 per cent hemoglobin. It is also noted, that only 21 women had a percentage of hemoglobin higher than 80.

TABLE II.—RED BLOOD CELL COUNTS IN TWO HUNDRED WOMEN EXAMINED DURING PREGNANCY.

Hemoglobin, per cent.	Average red blood cell count.	Number of cases.	Percentage.
90 or over	4,450,000	2	1.0
85 to 89	4,320,000	1	0.5
80 to 84	4,194,000	18	9.0
75 to 79	3,774,000	16	8.0
70 to 74	3,564,000	38	19.0
65 to 69	3,440,000	36	18.0
60 to 64	3,399,000	36	18.0
55 to 59	3,174,000	14	7.0
54 or lower	2,690,000	39	19.5
Total	200	100.0

Showing the averages of red blood cell counts according to the estimates of hemoglobin. Note that 163 (81.5 per cent) of the pregnant women gave hemoglobin estimates of 74 per cent or less and red blood cell counts averaging 3,564,000 or less.

Microscopic examination was made of the blood spreads of every patient. In the patients in whom the count was below 2.5 million, the erythrocytes showed the distinct changes of a severe anemia. Anisocytosis, poikilocytosis and polychromatophilia were frequently observed. Nucleated red cells were not found. It may here be mentioned that the color index was below 1 in every case of anemia studied.

TABLE III.—RELATION OF PARITY TO LOW ESTIMATES OF HEMOGLOBIN DURING PREGNANCY.

Previous pregnancies.	Number of estimates of hemoglobin recorded.	Number of estimates of hemoglobin under 75.	Percentages.
None	60	47	78.3
One	37	28	75.3
Two	31	27	87.0
Three	22	20	90.9
Four	11	8	73.7
Five or more	39	33	84.6
Total	200	163	81.5

Showing that parity was not related to the low hemoglobin estimates of 163 of the 200 pregnant women studied.

The patients with less than 75 per cent hemoglobin were classified according to the number of previous pregnancies, in order to ascertain the relationship between parity and the anemia. It is observed in Table III that 60 patients were pregnant for the first time, and

that 140 patients had had one or more earlier pregnancies. Of the 60 primigravidæ 47 (78.3 per cent) gave hemoglobin estimations under 75 per cent, whereas 116 (82.8 per cent) of the multigravidæ gave a percentage of hemoglobin under 75. It is evident that parity was not related to the low percentages of hemoglobin, since over 75 per cent in each age group had a deficient hemoglobin.

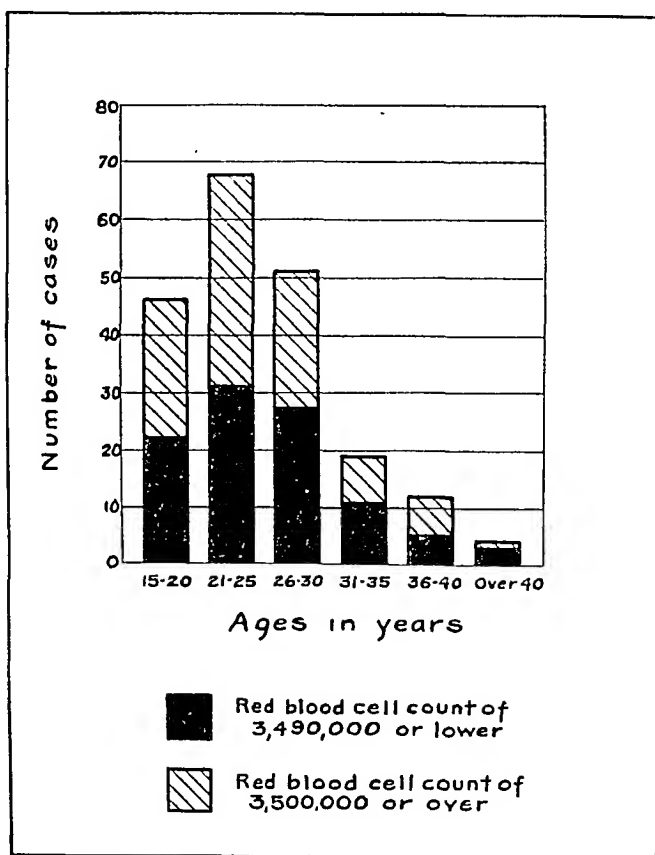


CHART I.—Red blood cell counts in 200 patients arranged according to age. Showing that approximately one-half of the women in each age group gave counts under 3.5 million cells, while the rest of them gave counts over this number.

Chart I records the number of patients according to age. It will be observed, that 165 (82.5) per cent of the patients were between fifteen and thirty years, and 35 (17.5 per cent) were over thirty years of age. Approximately one-half of the patients in each group gave counts of less than 3.5 million red cells. Inasmuch as 50 per cent of all the ward patients, regardless of age, gave red cell counts under 3.5 million, it would appear that age did not influence the incidence of moderate or severe anemia.

The systolic pressure was studied in order to disclose any possible relationship between blood pressure and the blood deficiency. The systolic pressure in 182 patients was available for study. Chart II shows that the systolic pressure in 136 patients was between 90 and

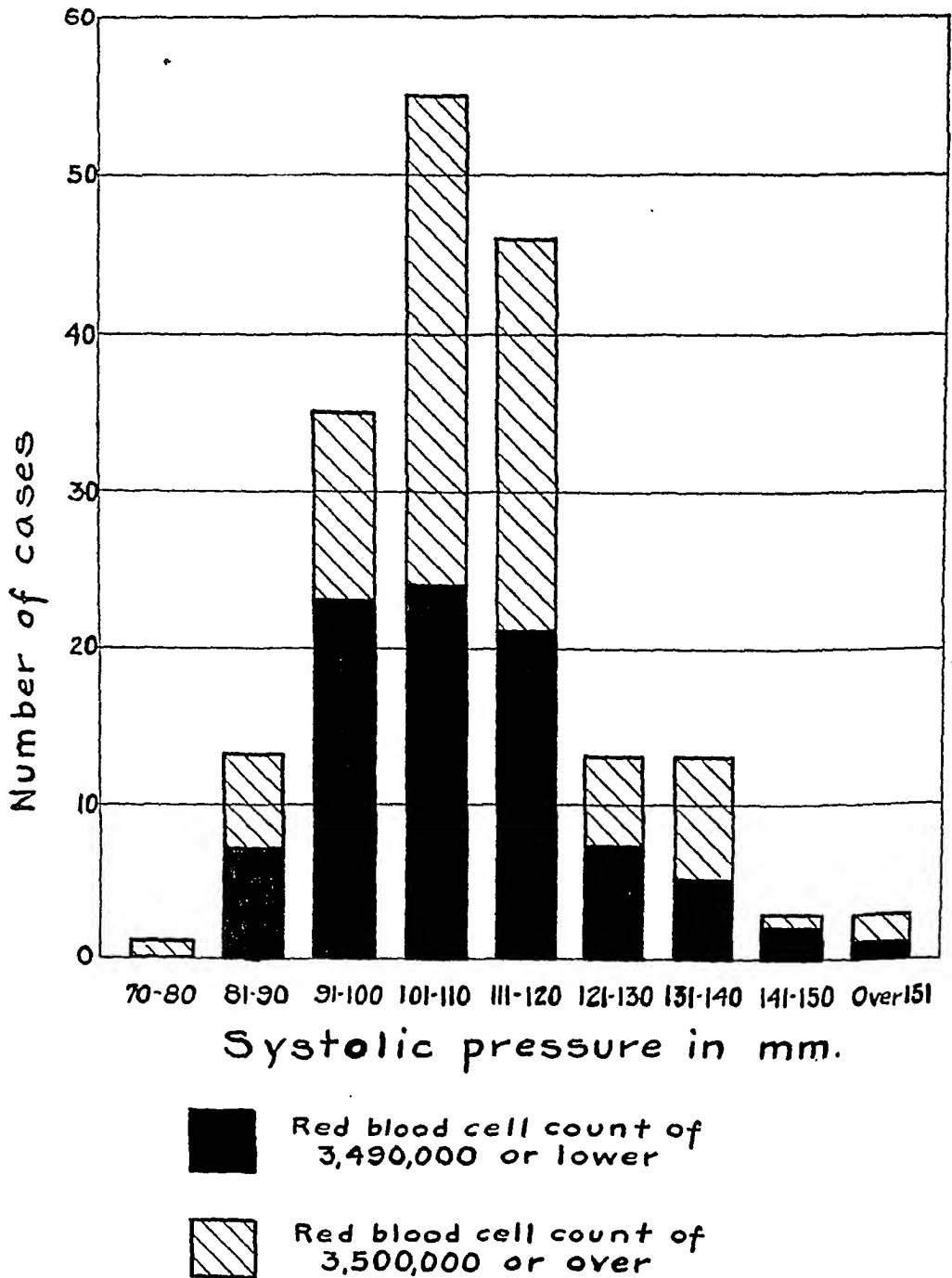


CHART II.—Red cell counts in 179 patients, arranged according to systolic blood pressure. Showing that most of the women had systolic pressures ranging between 91 and 120 mm., and that almost as many women in each blood-pressure group had counts below 3.5 million cells as had counts over 3.5 million.

120 mm. of mercury. In this group, 68 (50 per cent) had erythrocyte counts of over 3.5 million while the remaining 68 exhibited definite anemia (below 3.5 million cells). Approximately the same ratio (of counts under 3.5 million to counts over 3.5 million) existed in the groups of patients who presented a pressure below 90 mm. or above 120 mm. It is apparent that the systolic pressure did not influence the erythrocyte count during pregnancy.

Progress of the Anemia during Pregnancy. In order to determine the progress of the anemia with the advance of pregnancy, the blood counts in 35 patients made in the last month of pregnancy have been compared with the counts in these same patients prior to the eighth month. Thompson,⁵³ Sondern,⁵⁰ Osler⁴¹ and Bernhard⁸ found a distinct improvement in the anemia during the last two months of gestation. In a group of 42 women studied by Lyon,³⁴ 38 per cent showed an increase of hemoglobin in the third trimester, while 47 per cent exhibited a further diminution.

Fehling¹⁸ noted an average reduction of 0.7 million red cells, and of 7.8 per cent hemoglobin, in the last month of pregnancy. Kuehnel³¹ made erythrocyte counts every two weeks in 15 pregnant women, and found the anemia to be progressive during the first twenty-two weeks. After that, the condition would remain unchanged until the thirtieth week, at which time improvement would begin and continue after delivery.

TABLE IV.—STUDY OF THIRTY-FIVE PATIENTS SUBJECTED TO TWO RED BLOOD CELL COUNTS DURING PREGNANCY.

Number of patients.	Millions of red blood cells per c.mm. prior to eighth month of pregnancy.	Number of patients showing no change in counts at term.	Number of patients showing increase of 200,000 cells or more at term.	Number of patients showing reduction of 200,000 cells or more at term.
6	4.0 or over	0	1	5
13	3.5 to 3.90	5	3	5
12	3.0 to 3.49	1	7	4
4	2.5 to 2.99	1	3	0
35		7	14	14

Showing that increase and reduction in red blood cells at term occurred in equal number of cases. Thirteen of the women with definite anemia before the eighth month of pregnancy showed an improvement at term, while the anemia in 9 cases was more marked at term.

In our series of cases, shown in Table IV, 29 patients gave erythrocyte counts below 4 million prior to the eighth month of gestation. At term, 7 (25 per cent) of these manifested no change in the blood picture; 13 (44 per cent) showed an increase of 200,000 or more red cells per c.mm., whereas 9 (31 per cent) showed a decrease of 200,000 or more. The improvement noted in some cases is perhaps due to an attempt on the part of the bone marrow or other blood-forming organs to compensate for the apparent blood

destruction occurring in pregnancy. Diminution in the number of erythrocytes at term, is on the other hand, evidence of a more serious condition.

Course of Anemia in Puerperium. The effect of labor upon the anemia has been studied by numerous investigators. Terhola⁵² found a reduction in the erythrocytes and hemoglobin immediately after labor in one-half of his cases, with no definite change in the others. He observed that the red cell count tended to increase, in most cases, in four to eleven days after labor, and that it returned to the normal level in from one to four months after delivery.

Fehling,¹⁸ Rucker,⁴⁶ Given,²¹ Meyers,³⁵ Dubner¹⁶ and Sieben⁴⁹ also observed a diminution in the number of red cells shortly after labor, and attributed this loss to the hemorrhage and strain incident to labor. These authors noticed that a gradual increase in red cells and hemoglobin took place during the puerperium, and that the count at the end of two weeks was higher than during pregnancy.

Meyer³⁵ reported an average reduction of 750,000 red cells and of from 1 to 7.8 per cent of hemoglobin, immediately after delivery. He also attributed these changes to hemorrhage incident to labor.

Galloway,²⁰ in making counts on 33 patients during the first twelve days postpartum, found an average of 80 per cent of hemoglobin and 4.45 million red cells—a decided improvement over the findings during pregnancy.

The erythrocyte counts of 100 ward patients, made within forty-eight hours after delivery and again between seven and ten days after childbirth, were available for study. A comparison with the blood determinations of these same patients at term is shown in

TABLE V.—ERYTHROCYTE COUNTS IN PUERPERIUM.

Millions of red blood cells per c.mm. during last trimester.	Number of patients.	24 to 48 hours after labor.			7 to 10 days after labor.		
		Counts unchanged.	Counts reduced by over 200,000.	Counts increased by over 200,000.	Counts unchanged.	Counts reduced by over 200,000.	Counts increased by over 200,000.
4.0 or over . . . (Normal)	12	1	10 (83%)	1 (8%)	2	6 (50%)	4 (33%)
3.5 to 3.9 . . . (Slight anemia)	40	7	26 (65%)	7 (17%)	4	13 (32%)	23 (57%)
Below 3.5 . . . (Severe anemia)	48	12	8 (17%)	28 (58%)	5	9 (19%)	34 (71%)
Total . . .	100	20	44	36	11	28	61

Showing the number of patients who improved and did not improve within ten days after delivery. It will be observed that 57 of the 88 anemic patients improved in the puerperium, whereas one-half of the normal women showed lower counts during the puerperium.

Table V. It is to be noted that 12 of these patients approached term with a normal count (counts above 4 million), whereas 88 showed a definite anemia. Of the group with normal counts during pregnancy, 50 per cent manifested a definite reduction within ten days after delivery. Five of these women lost over 500,000 red cells per c.mm. The blood reduction in 2 of these 5 patients can be easily explained, as one suffered from late toxemia and was delivered by Cesarean section, while the other had developed an acute mastitis.

Of the 40 patients who exhibited a slight anemia at the end of pregnancy, 26 (65 per cent) showed a further diminution in the number of cells within two days after labor. We believe that the loss of blood incident to labor was responsible for this primary reduction in many of the patients. In 8 of the women, however, a reduction of over 500,000 red cells was noted within ten days after delivery. The complications, probably responsible for the severe loss of blood in 5 of these women were as follows: Two women had retained placenta with hemorrhage, 1 had a premature separation of the placenta, 1 had an acute mastitis, and 1 suffered from sapremia.

Of the 48 patients with a very severe form of anemia during gestation, 28 (58 per cent) improved within twelve to forty-eight hours after delivery, and 34 (71 per cent) within ten days. A reduction of over 500,000 cells was observed ten days after delivery in 5 patients, and was believed to be caused by acute appendicitis with appendectomy in 1 case, delivery by Cesarean section at term in 2 cases, acute mastitis in 1, and sapremia in 1.

The rapid recovery, occurring in the puerperium in many of the patients with a severe grade of anemia, seems to indicate that the expulsion of the fetus would stimulate the blood-forming organs to increased function.

Erythrocyte Counts and Hemoglobin Percentages Six Months after Delivery. The blood counts of 25 patients taken six months after delivery were available for comparison with counts made in pregnancy (Table VI). Of these 25 patients, 23 had presented a definite anemia during gestation, with hemoglobin percentages varying between 45 and 76. The improvement noted was definite. One patient with a previous normal count showed a slight anemia (Patient No. 4). The anemia in 4 patients remained practically unchanged, whereas a distinct improvement—manifested by an increase of over 200,000 erythrocytes—was found in 20 cases (87 per cent). Twelve of these patients, anemic during pregnancy, had red cell counts of over 4 million on examination six months after child-birth. One patient (No. 1) showed a fall in hemoglobin, probably due to a complicating mastitis. The remarkable improvement noted in these women six months after delivery suggests that factors associated with the pregnancy itself were responsible for the anemia.

TABLE VI.—ERYTHROCYTE COUNTS AND HEMOGLOBIN ESTIMATIONS IN TWENTY-FIVE PATIENTS DURING PREGNANCY, AND SIX MONTHS AFTER DELIVERY.

Number of patients.	During pregnancy.		Six months after delivery.	
	Hemoglobin, per cent.	Millions of erythrocytes per c.mm.	Hemoglobin, per cent.	Millions of erythrocytes per c.mm.
1	72	3.72	57	3.75
2	66	3.66	64	3.60
3	76	3.80	76	4.18
4	82	4.36	70	3.80
5	85	4.40	87	4.50
6	70	3.92	83	4.40
7	74	3.70	78	4.16
8	60	3.28	100	5.07
9	66	3.20	81	3.91
10	67	3.48	80	4.16
11	70	3.88	90	4.88
12	68	3.68	76	3.88
13	72	3.65	83	4.22
14	70	3.72	78	4.00
15	43	2.36	65	3.88
16	56	3.24	68	3.78
17	76	3.93	92	4.76
18	42	2.92	82	3.70
19	74	3.26	83	4.61
20	70	3.58	84	4.31
21	65	3.54	68	3.91
22	67	3.44	72	3.27
23	71	3.42	74	3.83
24	65	3.27	70	3.86
25	45	2.56	84	4.17

Showing the results of the blood examinations in 25 patients, made during pregnancy and six months after delivery. Note that improvement occurred in 20 of the 23 patients who manifested an anemia during pregnancy. In 1 patient (Case No. 2) the presence of mastitis may have prevented recovery from the anemia.

Comparison of Blood Counts in Ward and Private Patients. The results of examinations of 100 private maternity patients have been compared with those of the ward patients, in order to determine if environment and living conditions may have any bearing on the incidence of anemia in pregnancy. Since all of the private patients were examined at term, only those ward patients who had counts taken at term were selected for this comparison. The red cell counts and hemoglobin estimations of 179 ward patients were available for study.

The percentages of ward and private patients who gave hemoglobin estimations below 75 per cent are shown in Chart III. It is observed that about 62 per cent of the private patients had a hemoglobin percentage of less than 75, as compared with over 80 per cent of the ward patients.

Chart IV shows that over 40 per cent of the private patients gave normal counts, as compared with only 14 per cent of the ward patients. The percentage of ward patients having under 3.5 million

cells at term (52 per cent) was twice as great as that of private patients (26 per cent).

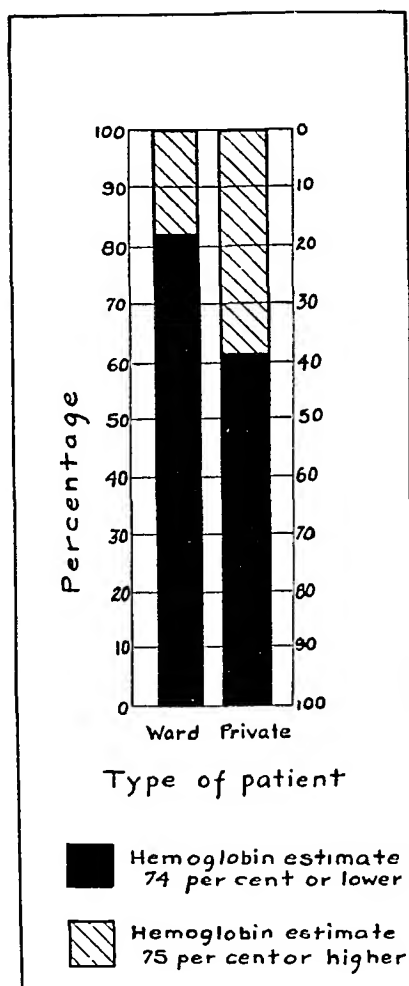


CHART III.—Percentages of private and ward-maternity patients presenting hemoglobin determinations of 74 per cent or lower, based on 200 ward and 100 private patients. Note that 82 per cent of ward patients and only 62 per cent of the private patients gave a low hemoglobin percentage.

The fact that so many private patients as well as ward patients were affected suggests that factors concerned directly with the pregnant state may have been responsible for the anemia. The influence of better environment and living conditions, however, may account for the lower percentage of private patients manifesting anemia.

Etiology of the Anemia. Several factors generally considered of importance in the causation of anemia were investigated. The importance attached to foci of infection directed our attention to the teeth, tonsils and urinary tract. Poor general health, toxemia and syphilis in the patients at the time of examination were also considered.

The result of this investigation is shown in Chart V.

Teeth were considered a source of infection in all cases in which dental caries or decay was evident. Chart V indicates that almost an equal number of women with "bad" teeth, gave counts above and below 3.5 million.

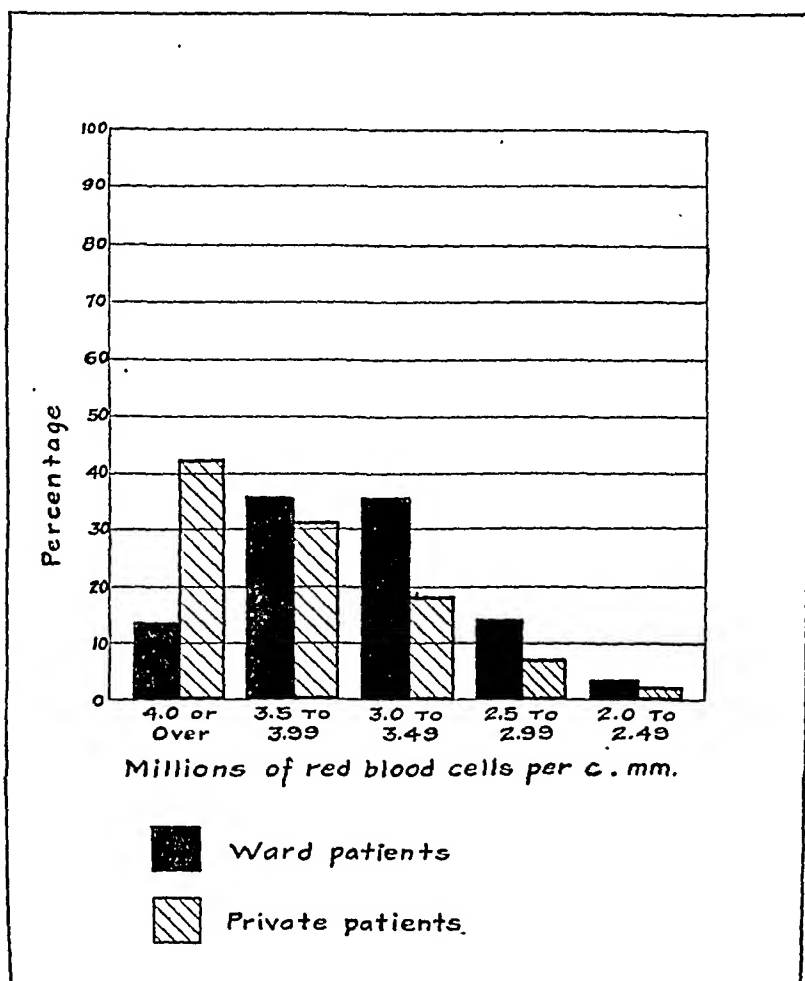


CHART IV.—Percentages of private and ward patients presenting various red cell counts, based on counts in 179 ward patients and 100 private patients at term. Note that only 14 per cent of the ward patients gave a count of 4 million or over, whereas 42 per cent of the private patients gave this count. It is observed that, for both classes, the percentages of patients having between 3.5 and 3.99 million cells are almost the same, while the percentages for ward patients having under 3.5 million cells is twice as high as for private patients.

Patients having enlarged tonsils, with a history of repeated attacks of sore throat, were considered to have infected tonsils. The study of the patients with infected tonsils brought forth results of an unexpected nature. The number of patients with supposedly infected tonsils with counts under 3.5 million was *less* than the number of these women with counts over 3.5 million.

The presence in the urine of 30 or more leukocytes per field, associated with urinary disturbances such as frequency or pain, was considered an indication of urinary-tract infection. It was realized, however, that an uncatheterized specimen did not necessarily depict the actual condition. Of 27 patients who showed over 30 leukocytes in the urine, 18 (67 per cent) had a count under 3.5 million cells. Assuming the above urinary finding to indicate infection, it would appear that involvement of the urinary tract was a contributory cause of the anemia in some of the cases.

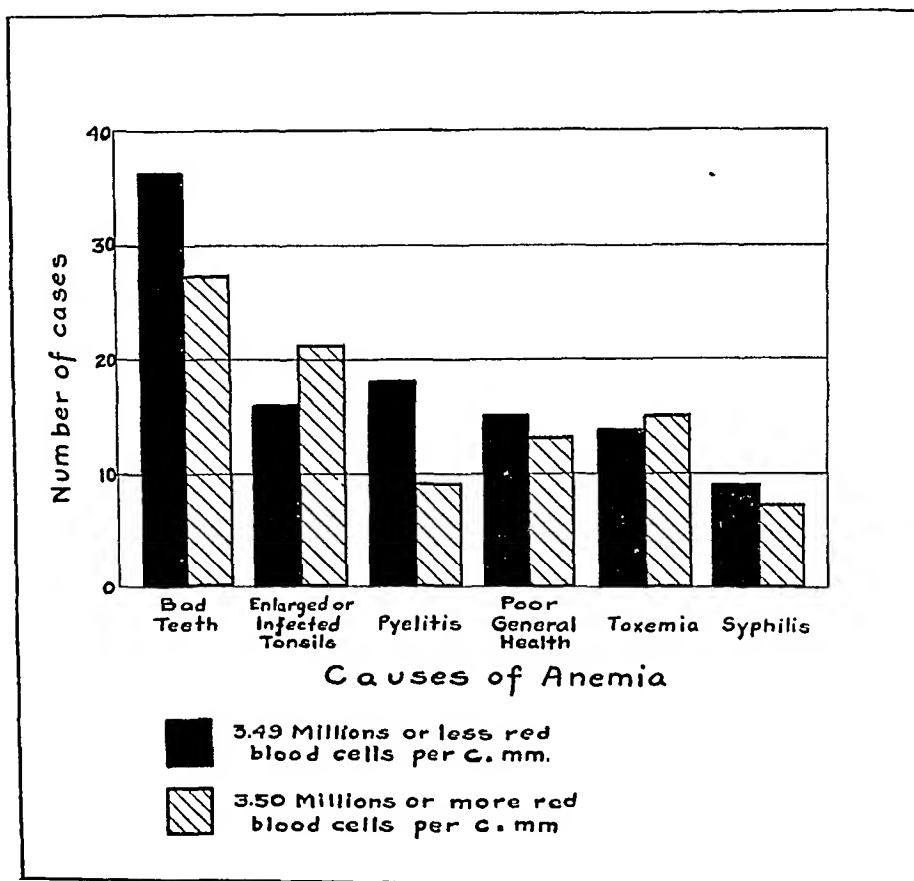


CHART V.—Classification of patients showing anemia, according to the causative factors investigated. Showing that twice as many patients with pyelitis had counts under 3.5 million as had over 3.5 million.

The general health was held to be impaired if the patient appeared to be in poor physical condition on examination, or if she complained of general weakness, insomnia, or dyspnea. The number of women in poor health who gave counts under 3.5 million was practically the same as the number who showed more than this number of cells. The state of health apparently exerted no influence on the blood condition in pregnancy.

Patients suffering from headache, exaggerated nausea and vomit-

ing, with a tendency to elevation of blood pressure (above 130 mm.), were considered as potentially toxic. Such toxemia apparently did not influence the blood picture, since the number of patients manifesting toxic symptoms was equally divided between the group showing anemia and the group not exhibiting an anemia.

A positive Wassermann reaction in a pregnant woman was taken as a criterion of syphilitic infection. Sixteen (8 per cent) of the 200 ward patients gave positive tests. The luetic patients all had erythrocyte counts under 4 million. However, the number of women with red cell counts over 3.5 million was almost as great as the number with less than 3.5 million. It cannot be admitted, therefore, that syphilis was a prominent factor in the causation of the anemia.

Discussion. The above consideration of possible etiologic factors throws no light on the actual cause of anemia in pregnancy. The specific cause of this secondary anemia remains unknown. Numerous theories have been advanced by various authors to explain the disorder. Audral and Gavarret,⁴ Regnault,⁴³ Becquerel and Rodier⁷ concluded from their studies that the reduction of erythrocytes during the course of pregnancy was of chlorotic origin. They believed that a true plethora did not exist in pregnancy, but that with an increase in the fluid content of the blood, there was a corresponding reduction in the number of red cells and in the iron content of these cells.

Willcocks⁵⁵ and Henderson²⁴ believed that the condition of the blood in healthy pregnant women did not constitute a true anemia, but was only a relative deficiency dependent upon the progressive enlargement of the vascular area during gestation, accounted for by the large increase in the water of the plasma.

Kiwisch²⁹ contended that there was a serous polyemia or hydremia in pregnancy which was brought about by increased glandular activity. The presence of a "plethora serosa" was denied by Scanzoni⁴⁷ and Cazeaux,¹¹ both of whom advanced the theory of a simple chloroanemia in pregnancy. They attributed to chlorosis the many functional disturbances which so frequently are associated with pregnancy.

Attention to "individual disposition" as the etiologic factor is mentioned by Peter,⁴² Fehling,¹⁸ Meyer,³⁵ Bernhard,⁸ Schroeder,⁴⁸ Adler,² Dubner¹⁶ and Reiml.⁴⁴ These authors maintained that healthy, well-nourished pregnant women have either a plethora or a normal blood condition, whereas the weak and undernourished women manifest a chlorosis. Ingerslev²⁷ also adheres to this belief, although he found counts of 5 million in the healthy as well as in the undernourished woman. Kuehnelt³¹ likewise reported the presence of anemia in the apparently full-blooded, as well as in the less robust individual.

Hofbauer^{25,26} believed that a syncytial hemolysin in the ectoder-

mal cells of the chorion was the cause of the maternal blood destruction in early pregnancy, and the increased iron content in the urine of pregnant women somewhat favors this theory of blood destruction. He contended that the physiologic anemia was overcome in the second half of pregnancy by an antihemolysin formed in the maternal blood but that if this function failed, an active hemolysis and progressive anemia would continue during pregnancy and after delivery.

Adler² held that the so-called 'pernicious anemia of pregnancy' occurred only on the basis of a primarily injured bone marrow. Sondern⁵⁰ found anemic gravid women in whom the usual causes of anemia, such as poor hygiene, nephritis, syphilis and tuberculosis, were not present. Lyon maintained that the anemia of pregnancy represented a preëxisting anemia which had continued in pregnancy, since he observed a similar anemia in a group of nonpregnant women with retroversion of the uterus.

Certain facts brought forth by this study have convinced the authors that factors, as yet unknown, connected with the gravid state are, directly or indirectly, responsible for the anemic condition so frequently observed in pregnant women. The fact that the private patient coming from an environment conducive to good health manifested an anemia, although not as severe as the ward patient coming from unfavorable surroundings, indicates that the pregnancy *per se* in some manner had produced the blood deficiency.

The assertion that only a relative anemia exists in pregnancy is a disputed matter. It is generally recognized, that the vascular area is considerably and progressively enlarged in pregnancy because of the increase in the water content of the plasm. If one assumes that the number of erythrocytes is not diminished in pregnancy, then the dilution of the blood which occurs as a result of the increased enlargement of the vascular system would manifest itself in a lowered cell count. A relative anemia would then be the natural result.

The spontaneous recovery, ensuing in most cases within ten days to six months after delivery, points to a return of the maternal circulation to the volume of the nonpregnant state. The improvement also indicates that the anemia did not exist prior to the onset of pregnancy. It is conceivable, however, that some of the patients who became more anemic within ten days after delivery may have been deficient in blood before the beginning of gestation. Complications of labor or of puerperium, associated with hemorrhage or sepsis, were uncovered in several of our patients who did not improve after labor. Thorough examination of recently delivered women, in whom the anemia persists, may disclose causative factors similar in nature to the ones found in several of our patients.

Patients with hemoglobin determinations below 75 per cent and red cell counts under 3.5 million should be particularly observed, and therapeutic measures instituted immediately upon discovery of

deficiency. These patients should be watched for several months after delivery, and microscopic blood studies made in order to secure evidence of beginning bone-marrow changes.

Summary and Conclusions. The following facts and observations were brought out by this investigation:

1. Of 200 ward maternity patients, one-half exhibited a definite anemia during pregnancy, with red cell counts below 3.5 million per c.mm. Of 100 private patients at term, 26 per cent gave counts below 3.5 million. It was found that 126 (42 per cent) of the entire group of 300 gravid women studied, regardless of the time of examination, gave counts below 3.5 million cells.

2. It was found that 82 per cent of the 200 ward cases, and 62 of the 100 private maternity patients, gave determinations of hemoglobin of 74 per cent or less.

3. The severity of the anemia is apparently not affected by parity, age, or blood pressure.

4. No conclusive evidence was discovered to confirm or disprove the contention of other authors that improvement occurs at term. In a study of 35 patients, having two blood determinations in pregnancy, we found in 14 a gain of 200,000 cells or more and a reduction of the same number of cells in 14 others.

5. Several etiologic factors, including ill-health, foci of infection, toxemia and syphilis, were investigated, but the extent of their influence was not sufficient to be determined.

6. The most interesting fact disclosed by this study was the remarkable and rapid recovery occurring in a large number of women within a few days after delivery. It was found that 34 of 48 women (71 per cent), having red cell counts below 3.5 million in the last trimester of pregnancy, gained over 200,000 cells per c.mm. within ten days after delivery. Of 23 patients, definitely anemic during pregnancy, 20 were observed to have practically fully recovered in six months after delivery.

7. The large percentage of private patients with anemia indicates that environmental circumstances alone were not responsible for the anemia.

8. The etiology of the anemia of pregnancy remains undisclosed. The withdrawal of iron from the maternal corpuscles by the fetus, the existing hydremia of pregnancy, and a preëxisting chlorosis, all these are probable factors in its production. Further investigation is required to throw light on the fundamental nature of the secondary or so-called physiologic anemia of pregnancy.

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ANEMIA OF THE NEWBORN.

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In the last few years several authors have written of a rare form of anemia, the anemia of the newborn. Six cases have been reported one each by Ecklin,¹ Donally,² Susstrunk,³ Sanford,⁴ Bonar⁵ and McClelland.⁶ The case to be described conforms to the others in most respects, with certain exceptions to be noted later. Though

only recognized recently, it is probably a rare condition. Even those infants which are soon to become anemic, have, as Lichtenstein⁷ has shown a normal blood picture at birth.

Case Report. *History.* N. H., a girl, white, was born March 20, 1929. This was the first pregnancy. Labor was induced a few days before the expected time of confinement because the mother had hypertension, albuminuria and some toxemia. A chronic cholecystitis had been diagnosed during pregnancy. The mother's blood count on the day of delivery was as follows: Leukocytes, 12,000; erythrocytes, 3,930,000; hemoglobin, 74 per cent; polymorphonuclear neutrophils, 79 per cent; lymphocytes, 21 per cent. The delivery was instrumental, high forceps being used. The birth weight was 5 pounds 9½ ounces. The infant was first seen on March 21, when two days old.

Examination. The infant was small, pale and listless, with a shrill cry. The anterior fontanelle was quite tense and slightly bulging. There was no jaundice. The skin and mucous membranes were strikingly pale. The pupils were equal and reacted to light. The heart and lungs were normal. The abdomen was not distended and neither liver nor spleen could be palpated. The lower extremities were rigid and the reflexes hyperactive. A lumbar puncture revealed a blood-tinged fluid and 5 cc. was removed. The fontanelle was then found to be less tense and somewhat depressed. A blood examination at this time (March 21) was as follows: erythrocytes, 1,780,000; hemoglobin, 48 per cent; color index, 1.3—; leukocytes, 17,000; polymorphonuclear neutrophils, 76 per cent; lymphocytes, 18 per cent; mononuclears, 5 per cent; eosinophils, 1 per cent; blood platelets, 260,000. There were a few nucleated red cells and moderate anisocytosis. The patient and father were both in Group 1.

On the third day after birth (March 22) 100 cc. of whole blood from the father was given to the patient. There was no reaction and no rise in temperature. On March 23, the day after transfusion, the blood count was as follows: erythrocytes, 4,150,000; hemoglobin, 80 per cent; color index, 1—, leukocytes, 9400; platelets, 320,000; polymorphonuclear neutrophils, 74 per cent; lymphocytes, 25 per cent; eosinophils, 1 per cent. The patient was much brighter, the color was good. There was no evidence of cerebral irritation and the fontanelle was soft. Feedings were taken fairly well. Three days after transfusion the erythrocytes were 5,370,000 and the hemoglobin was 90 per cent. At no time was the spleen felt. The infant appeared normal in every respect. At the age of four months the blood was examined again and the erythrocytes were 4,500,000 and the hemoglobin 80 per cent. The weight was eleven pounds. The color was good and the infant was bright and active. The spleen could not be palpated.

Comment.—The etiology of anemia of the newborn is obscure. A possible cause in this case (hypertension, albuminuria and toxemia in the mother) cannot be ignored, although the mother was not particularly anemic. Bland and Goldstein⁸ have recently shown that 50 per cent of pregnant women have erythrocyte counts below 3.5 million per c.mm. This anemia is only temporary as 92 per cent of 50 patients showing anemia in pregnancy made a spontaneous recovery within six months after delivery. Toxemias of pregnancy in the mother do not usually cause severe anemia in the

newborn, and the rarity of such anemias would indicate that there is some other factor responsible. This is the only case reported where the mother had hypertension and toxemia. There is also the possibility that the anemia was due to intracranial hemorrhage. The spinal fluid was blood-stained and the fontanelle tense. However, after one lumbar puncture the infant's condition was so much improved that no further treatment was necessary. The hemorrhage, therefore, could not have been large. It is interesting to note that in the case reported by Donally, there were signs of cerebral hemorrhage. A slight cerebral hemorrhage in the newborn does not cause as severe an anemia as was present in my patient. The other causes of anemia in the newborn can be ruled out. At no time was there bleeding from the mucous membranes, purpuric spots, or jaundice. There was no evidence of tuberculosis or syphilis. There was no fever at any time or signs of sepsis.

Summary.—It would seem that anemia of the newborn is a definite clinical entity, as evidenced by the similar blood picture in all the reported cases, the good prognosis and the permanent improvement after the infant reaches the second half of the first year. The true etiology is probably to be found in some temporary defect in the blood-forming tissue of the infant, but this is only conjecture. The recovery of infants with this type of anemia is usually complete in a few months. In the cases described by Ecklin, Sanford and Bonar, recovery was effected without blood transfusion. This proves that there is no permanent injury of the blood-forming organs. Only one case has proved fatal (Susstrunk) and here autopsy failed to reveal the cause of the disease. Anemia of the newborn is similar to hemorrhagic disease of the newborn in that the blood defect in each disease is temporary and recovery may occur without treatment. Blood transfusion in anemia of the newborn is the treatment of choice and in my patient produced an immediate cure.

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THE ECZEMA PROBLEM.*

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NOT all dermatology concerns itself with polysyllabic rarities of small moment to medicine as a whole, or with the minor surgery of cosmetic blemishes. Within the field lie some of the crippling ills of mankind. Eczema, in certain senses of the term, is one of these, and to its study at this moment a generous share of energy and brain power is being devoted. It evidently occurred to your secretary, as to me, that you would be interested in a statement of our present position in regard to this problem.

First let me attempt a redefinition of the term eczema in line with current conceptions of the trend of dermatology away from the purely descriptive toward the more fundamentally etiologic viewpoint. Eczema is a dermatitis, a catarrhal cutaneous inflammation in which exudation or secretion of fluid is a conspicuous feature. Does this quality justify the separation of eczema from the multitude of other forms of dermatitis? I believe not. Inflammation, with its fundamental pathologic reaction signs, is simply a form of sign language, a cry of protest, aroused by etiologic stimuli, and in the end classifiable best on the basis of the stimuli, rather than, figuratively speaking, on the minor tonal and pitch variations of the cry. Before defining eczema, then, let us attempt an etiologic definition of dermatitis, for the causes of dermatitis embrace those of eczema. A dermatitis is a cutaneous inflammation aroused by the interaction of two groups of causes, constituting a foreground and a background of the picture; predisposing causes, largely in the constitutional background, and exciting causes, the immediate usually irritant accidents or contacts. The exciting cause, if I may quote myself and change the metaphor, acts as the trigger pull to the already existing load of predisposing causes, and the result of that interaction is a cutaneous explosion in some one or other of the many inflammatory forms, ranging from hives to eczema.

It follows, then, that a thoroughgoing and sometimes highly complicated analysis must precede the therapeutic decision in each individual case of dermatitis, if lasting good results are to be secured, in the effort to unravel the interaction of predisposing and exciting causes and to apply the proper treatment to each. In order to assist my students in this process, I have prepared an analysis of present knowledge on this subject, given in the body of this text. In a sense this analysis constitutes a species of desk card, against

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which the case before one can be analyzed as the patient is questioned and studied.

THE CAUSES OF DERMATITIS.

I. *Two Groups.* *Predisposing causes*, which form the constitutional background, on which dermatitis develops, and *exciting causes*, the immediate, usually irritant accidents which precipitate the cutaneous explosion, acting as a "trigger to the charge of predisposing causes."

II. *The Predisposing Causes.*

1. *Race.* Blonds predisposed. Neurotic racial strains.

2. *Age.*

(a) *Infancy and Childhood.* Predisposed to the allergic eczemas, the superficial pyogens, the exanthems, the scalp ringworms, animal parasites.

(b) *Prepuberal and Puberal Years.* In addition to the above, the seborrheas, psoriasis.

(c) *Young Adult Life.* The epidermophyton ringworms of feet, groins, hands, seborrheic dermatitis, lymphomatosis.

(d) *After Thirty-five Years.* The occupational dermatitides, eczematoid dermatitis, seborrheic dermatitis, cutaneous neuroses, lymphomatoses.

(e) *After Fifty Years.* Involution dermatitis, a complex of decreased elimination, accumulating infections, nervous overload and so forth.

3. *Infection.*

Focal. Teeth, tonsils, sinuses, appendix, bronchiectatic conditions, gall bladder, colon, prostate, cervix.

Systemic Associations. Intestinal parasitism (ascaris) and dermatitis, variola and pyogenic infection, streptococcal and staphylococcal septicemia and the purpuras, toxic erythemas and erythema multiforme group.

Local. Abscesses, draining sinuses, suppurations, etc.

4. *Parasites.* Pediculosis, scabies, postscabetic sensitization. More rarely, mosquitoes, bedbugs, straw mattress mites, fleas, chiggers.

5. *Neoplasms.* Lymphomas, leukemias. Various neoplasms, through invasion of the liver or obstruction of the biliary tract, with the production of jaundice.

6. *Abnormalities in Blood Chemistry.* While much studied and theorized about, abnormalities in blood chemistry are few in dermatitis and of doubtful etiologic significance. This includes sugar, chlorids, uric acid, nonprotein nitrogen and calcium. Photosensitive substances; hematoporphyrin the only known example.

7. *Disturbances of Diet.* High carbohydrates especially; rest and exercise.

8. *Disturbances of Intake-output Ratio.* Metabolic effects of overeating, underexercise and waste retention (nephritis, constipation).

9. *Gastrointestinal Disturbance as Such.* Hypochlorhydria and achlorhydria, colitis, colonic and intestinal stasis, spasm and spastic disturbances.

10. *Excessive Sexual Activity and the Puberal State.* Pyogenic and seborrheic lesions.

11. *General Sensitivity*. Indefinable by our present knowledge. Due to proteins? Histamines? Bacterial decomposition products? Intestinal disturbances? Vagotonia? Vasomotor instabilities? Pluriglandular syndromes?
12. *Nervous Overload and Disturbance*. Including sexual complexes, inferiority complexes, anxiety neuroses, and so forth. Acts through:
 - (a) Endocrins (thyroid and adrenals).
 - (b) Vasomotor mechanism (rosacea, urticaria).
 - (c) Sympathetic-vagus system (urticarias, rosacea, neurogenous dermatitis). Includes action on digestive secretions, intestinal peristalsis, etc.
 - (d) The sensory mechanism of itching (unknown).
13. *Endocrin Abnormality as Such*. Low basal-metabolic rate. Hypothyroidism. Menstrual disorders, especially amenorrhea.
14. *Cutaneous Dystrophies and Functional Abnormalities*.
 - (a) *The Ichthyotic State*. Dry skin, slightly scaling forehead and scalp, pretibial region, follicular plugging of the extensors, parchment palms.
 - (b) *Seborrhea*. Hyperactivity of the sebaceous glands. An endocrin background (?).
 - (c) *Hyperidrosis*. Perspiring palms, soles, scrotum, axillæ. A "sympathetic" neurosis (?).
 - (d) *Vascular stasis*.
 1. Vasomotor (rosacea, blue hands and feet and so forth).
 2. Mechanical (varicose and thrombotic).

III. *Exciting Causes*.

1. *External Irritants*.
 - Occupational contacts.
 - Drugs and medicaments.
 - Chemicals.
 - Cosmetics.
 - Vegetable poisons (Rhus, and so forth).
 - Light, heat and cold. Mechanical agents (friction).
2. *Allergy-producing or Exciting Agents*.
 - (a) *Specific*. Food and other proteins, pollens, plants, animal products (hair, fur and so forth).
 - (b) *General*. Serums, bacterial toxins, vaccines.
3. *Infections*.
 - (a) Ringworms (dermatophytids, in which the organism is not present).
 - (b) Streptococcus and staphylococcus infections, local and general.
4. *Parasites*.
5. *Trauma*.
6. *Nervous shock*.

If then, etiologically speaking, this be dermatitis, what is eczema? Over this question, which brings to a focus all the problems of direct and indirect etiology, the battle still rages. A powerful and extremely modern group, with whom, it must be conceded, rest many of the laurels of distinctive scientific achievement, insists that extrinsic or exciting cause and not constitutional background is the etiologic force and fact in eczema as it is in dermatitis. There is, therefore, according to this group, no difference between eczema

and dermatitis, etiologically or pathologically. A second group, for whom Pulay has been a recent spokesman, insists that eczema is fundamentally a constitutional disease and that, whatever the exciting cause that may be unearthed, it reacts upon an essential and indispensable susceptible background. Moreover (and here is the crux of the issue), an eczema persists and may extend, it is contended, even after the removal of the determined exciting cause—the best evidence of the potency of the constitutional element.

After all, it seems to me both groups are in a sense right, and that the apparent disagreement is more a matter of relative emphasis than of fact. A compromise position can be stated which allows both sides their due. I, therefore, for the purposes of discussion, define eczema to you as:

“A form of dermatitis in which the constitutional background has come to outweigh the exciting cause, though both are present at the outset, and may continue present throughout the picture.”

On the other hand, as Pulay puts it, irreversible changes may occur in the skin, or it may be so predisposed by the patient's inherited constitution that the dermatitic process is perpetuated as eczema, even after the withdrawal of the extrinsic exciting cause.

Crudely speaking, one may illustrate this difference by example. A given person in ordinarily good general health may sit down in, or handle poison ivy, and develop the typical picture of a dermatitis venenata, which subsides under ordinary soothing treatment in ten days. A second person with a background of predisposing causes develops poison ivy under the same conditions and at the same time, and in his case the process not only does not subside in ten weeks, instead of ten days, but it spreads to other parts of his body, which have had no contact with the irritant oil as such. Months after the removal of the exciting cause he is still suffering from extensive patches of eczema which respond, if at all, only to measures that fundamentally change not only the physicochemical background of his skin but the autonomic-sympathetic balance of his nervous system, the cellular reactions of his body tissues, the behavior of his hematopoietic system, the reactions of his gastrointestinal tract and even his whole outlook on life. In the process of readjusting this fundamental constitutional background, everything may have failed until with the extraction of an infected tooth, the drainage of an antrum, the removal of an infected gall bladder or the reëducation of the patient with respect to a mother-in-law, the whole process has begun to mend, and has stayed mended so long as the individual remains in balance with his predisposing background. He may remain susceptible to poison ivy, but an attack will clear up comparatively rapidly until his constitutional ledger again shows a debit. Then he will have another siege of “eczema,” to be dealt with in the same way.

I am sure it will be apparent to you, then, that the study of

the etiology of eczema will carry us far afield, into a variety of medical problems, among the foremost of which will be those of allergy or hypersensitivity, in which so many important advances have been scored in the last few years by Jadassohn, Coca, Zinsser, Doerr, Bloch and their students and co-workers. There is a tremendously convincing quality about a demonstration such as the Prausnitz-Kustner or the Walzer technique of predicating the presence of an antigen in the blood serum of the susceptible individual, responsible for an interaction between the offending external substance or cause, and the patient's tissues; an antigen which has the highest degree of specificity for the incriminated substance. Such demonstrations rightly give the claim of the "externalists," who insist that every dermatitis and eczema has an extrinsic cause, a remarkable degree of force and convincing quality. Under the influence of this school of thought innumerable substances, toxins, organisms and contacts have been found to produce dermatitis and to underlie what had previously been regarded as eczema of exclusively internal or intrinsic causation. Today, the list of exciting causes which the conscientious and well-equipped dermatologist must be prepared to hunt down in any given case ranges from the ink of the Sunday rotogravure supplement and the celluloid rim of the eyeglass to the hair of the son's pet guinea pig, the fungus between the patient's fourth and fifth toes, the plant on his dining-room table, the seasoning in his soup or the roundworm in his gut. One look at a rubber shoe heel containing hexamethylene as a catalyzer will send the workmen of a factory into frenzies of dermatitic protest. Steam-distilled is alleged to differ from old-fashioned turpentine. Though a man may not, by Holy Writ, live by bread alone, it appears that he may have eczema by it alone and fill the columns of the German literature with dissertations on bakers' dermatitis. Though I seem to use a facetious tone, I say in all sincerity, more power to the discoverers of exciting causes. They have at least convinced us of the eminent worthwhileness of determined search of the visible and contact world for the explanation of a dermatitis or an eczema. Such a search should always be made before we proceed to appraise the internal, the invisible and the as yet to some extent speculative elements which go to make up the constitutional background suggested as the line of differentiation between dermatitis and eczema. On pain of being declared lazy then, let us not neglect the thorough search of our patient with eczema for the external causes of the dermatitis which afflicts him.

But shall we stop there? Is there not something suspicious about this amazing accumulation of external irritants which will set someone somewhere into cutaneous spasms? Is it in keeping with our general knowledge of the plastic interaction that occurs between parasite and host, between donor and recipient, between this human

protoplasmic gel and the agents that creep and crawl across it or push and prod against it, that there should be no internal predisposing reactive mechanism to be studied in connection with the effect of an irritant coming from without? Is it not conceivable that study of the reactor may disclose a nonspecific as well as this startlingly specific mechanism of reaction which has so usurped our recent attention? To this point of view the eminent British student of occupational dermatoses, Prosser White, I think it was, led the way in linking to the local effects of industrial irritants, a systemic predisposing background, including therein the effects of age and worry and of the seborrhoeic makeup, grounded as it is in the carbohydrate metabolism. To these more obvious elements the school of Kreibich and such observers on the neuropsychiatric borderline as Sack are adding a neurogenous background. The studies of Klauder on the calcium-potassium balance in its effect on the vagus-sympathetic system, while still on chemically unstable ground, are giving some elements of tangibility to the hypotheses centered around that *terra incognita* of the human being, his vegetative nervous system. Bloch is undoubtedly right in asserting that the tangibilities are on the side of the externalists and that they are advancing much faster for the moment in their share of the working out of the etiologic mechanism of dermatitis and eczema. The students of intrinsic causes, the scientific as distinguished from the intuitional side of whose work is so fraught with pitfalls of subjectivity and experimental difficulties, are still far in the rear. But there is no justification for a refusal of either side to recognize the existence of the other, or for the specifists to deny the influence of a general predisposing mechanism among the causes, merely because mental stress, for example, is not as visible and measurable as the dose of primrose extract which will induce sensitivity in a normal and previously unsusceptible subject.

What then is the eczema problem of today? It consists in an effort to unravel the details and to make a statement of the laws governing the specific reactivity of an individual to the exciting cause coming from without which is giving him or has given him an eczema; and an equally clear definition of the type and methods of action of the *internal* disorders and disturbances of function and structure which contribute to and perpetuate his abnormal reactivity to stimuli, specific or nonspecific.

Turning then once again to the schedule of causes of dermatitis, one finds therein many evidences of the sifting-out process with respect to the older conceptions of eczema, that today confuses the practitioner whose dermatology dates back twenty or even ten years. Many things that passed as eczema in the texts and teachings of only a decade ago are now being recovered from the catch-basket and pigeonholed as well-defined entities. This is particularly true of dermatitic reactions due to infections. The best

examples lie in the field of the mycotic or fungous lesions of the skin. Many of the former "chronic eczemas" of the hands and feet are now recognized either as actually due to a fungus, usually some member of the epidermophyton group of fungi or as secondary sensitization phenomena, spoken of as dermatophytids. The eczemas of the axillæ, groins and anogenital region, known for years as intertrigoes or flexural eczemas, are falling into the same group. Castellani among others has given much attention to these types. The moist and freely-perspiring regions of the body, and particularly those whose sweat and circulatory mechanism is markedly influenced by states of nervous stress or excitement, are ideal sites for the development of mycotic eczemas. In some of their forms, as particularly in the so-called eczematoid parakeratosis, which affects the submammary and inguinal regions of elderly women, with frequent coincident involvement of the skin behind the ears and in the umbilical depression, the instrumentality of a fungus or of some infectious agent seems almost undoubted. The clinical picture is as distinct an entity as herpes zoster. Culture, however, may fail to identify anything but a mixture of pyogenic organisms, often unusual types of streptococci, possibly because of unsuitable media or growth conditions.

Evidently, then, the bacterial and mycotic flora of eczema is a problem of the first order; to be studied, let me insist again, from the standpoint of the favoring conditions in the patient which promote such growth and such distinctive localization, quite as much as the classification and type of the organism. In the one direction, as evidence of the trend of the time, we find the observations of MacLeod and his co-workers in England, and of Cleveland White and C. J. White and others in this country, tending to indicate that what have been called seborrheic eczemas are yeast infections on a susceptible background. The observations of Fordyce, Sutton, and recently of Herbert Mitchell, on the other hand, point toward pyogenic organisms as responsible for other distinct types of what used to be eczema, particularly of the extremities. The newer terminology, then, should recognize a concept within the old "eczema" category. This is "eczematoid dermatitis," of mycotic (yeast) or infectious (pyogenic) origin. The former group includes attendant allergic phenomena in specially susceptible individuals and the latter includes eczemas apparently traceable to pyogenic organisms, yet without the distinctive pustulation, crust and bulla formation of the impetigoes. The whole problem is complicated by the question of contaminants and saprophytes as against pathogenic organisms. A number of years will probably be required to establish conclusively the causative as distinguished from the merely coincidental or contributory rôle of some of the microorganisms now put forward as responsible for various forms of dermatitis and eczema. Be that as it may, the group of infectious eczematoid

dermatitides is the most recent branch from the ancient parent trunk of eczema. The importance of the factor of individual constitutional background even in this new group is well illustrated by the fact that certain of the investigators mentioned have been successful in their attempts to carry through the postulates of Koch, only by inoculation upon the skins of the patients who were already victims of the "eczema" they were investigating. Normal skins, as noted by both MacLeod and White, do not give typical lesions on inoculation of cultures. Even here, then, the constitutional background outweighs the external exciting cause.

In the background of eczematoid dermatitis, as I have seen it, lie the elements of a disordered cutaneous carbohydrate metabolism or an excessive carbohydrate intake; the congenital anomaly of the fat secretion mechanism and the keratization cycle known as ichthyosis; gastrointestinal dysfunction, especially hypochlorhydria; elements of nervous stress, fatigue, overwork and strain; focal infections in tonsils, teeth, sinuses, colon, gall bladder or perhaps prostate; allergic elements, including susceptibility to special irritants and the atopy to be presently mentioned as occurring in true diathetic eczemas.

With intertriginous eczema, seborrheic eczema and infectious eczematoid dermatitis being gradually reinterpreted with respect to their balance of constitutional and external exciting causes by an increasing clarification of the local factors, there remain to be accounted for under the general concept of eczema, the so-called nurslings' eczema of the German writers; metabolic eczema; involution eczema and, finally, neurogenous eczema and the so-called diathetic or constitutional eczema which forms the third member of the eczema-asthma-hay-fever complex. In these groups the constitutional background still appears to maintain the upper hand in the etiology.

The term infantile eczema, as commonly used in this country, covers a variety of types. The seborrheic or carbohydrate metabolism factor is chiefly responsible for one group, which responds to a reduction in starch and sugar intake and a substitution of fats. Essentially this is seborrheic eczema in the child, then, from the constitutional standpoint. Another group of infantile eczema cases undoubtedly can be classified as infectious eczematoid dermatitis—the pustular pictures which are not impetiginous, the extensive, even universal eczemas of infancy with marked lymph-node involvement and occasional abscess formation or alternating bouts of multiple furunculosis and eczema. A third group includes the allergic eczemas, in which cutaneous tests demonstrate a reactivity to certain food proteins, notably those of milk, beef, eggs and wheat, and from which recovery takes place on withdrawal of the incriminated substance. This last-mentioned is perhaps the true nurslings' eczema of the German writers. The term infantile eczema,

as used in this country, includes all of them and success in their management is to some extent dependent on ability to identify the most influential factor by a careful local and general examination and a detailed dietary and habit history. Close on the borderline of infantile eczema lies that most interesting complex of dermatology in children, a curious mixture of eczema, urticaria and erythema multiforme, called lichen urticatus, in which neurogenous factors mingle with local, dietetic, infection and sensitization elements in a most intriguing interplay. Included in what is commonly called infantile eczema is, too, a proportion of cases which represent the early symptomatic appearance of the true diathetic eczema to be presently described.

Metabolic eczema is a concept of decidedly hazy definition, and one more often, I think, misused than correctly applied. A typical example would be the type of eczematous and dermatitic change which is seen most often in young girls in association with subnormal basal metabolic rates indicative of endocrin deficiencies. The response of some of these patients to thyroid medication is undoubted. But as one observes a succession of them, one wonders whether it is the thyroid as such that brings about the improvement, if any occurs, or whether it is not simply the action of the drug as a vasodilator, with the consequent stimulation of the keratization cycle of the skin, and the raising of its general nutrition through a freer blood supply, rather than a distinctive endocrin action as such. Undoubted cases of ichthyosis in young persons, for example, can be transiently improved by the administration of thyroid, which makes them sweat—but if the drug be continued they quickly show signs of hyperthyroidism, as would a normal person, and if it be dropped they recur to the original cutaneous condition. The action would in such cases seem to be incidental and symptomatic rather than fundamental. That there is a metabolic element in many eczemas seems probable, but that it is causative of the cutaneous picture, and not merely another symptom of some underlying disturbance, probably of the sympathetic nervous system, is the impression one gets from repeatedly working up such cases. The significance of the basal rate of -4 to -14 in these patients, so often stressed by internists venturing into dermatology, together with the disturbance of gastric secretion in the direction usually of hypoacidity; the low blood pressure; the irregular menstruation, alternately retarded and overfrequent for considerable periods; the vasomotor instabilities; the occasional suggestion of acromegaly—all these things point toward endocrin disturbance. Their intimate significance, however, so far as thyroid, pituitary and other endocrin glands are concerned, is as yet far from explanation. There are undoubtedly metabolic factors in eczema, but their meaning is still obscure.

Involution eczema includes the intractable dermatitides of later

life, which so much too often torment what should be a peaceful old age. Here, too, is a field full of problems, and no entity is precisely definable. The ears, scalp, groins and extremities are most often involved. A search for every available external irritant explanation in these cases often leaves one with nothing tangible. The patient is simply old and worn out. Focal infections may be identified, but there is no result from their removal, the trouble being simply transferred to some other point in the patient's weakened economy. Time and again it has seemed to me, for example, that the chronic bronchitis superposed on emphysema in the aged in this climate, is an important element in the irritable senile skin. Physiologic decline of the fat-secreting power of the sebaceous glands leaves the skin relatively more susceptible to bacteria and external irritants. Winter drying and artificial heat, toothless mouths that cannot chew food, senile achlorhydria, the train of prostatic difficulties, the chronic joint focus, the ancient and honorable "gouty diathesis," all mingle in a depressing background of decay. One is tempted again and again to write a thesis upon *worry* as the background for the itching skin and scratcher's dermatitis of old age. Yet it is imperative to resist the temptation to fall back on generalities until every individual item of local importance has been accounted for. How often have I been inclined to accept involution eczema as a diagnosis, ultimately to find that bandage support of a mild grade of varicose veins did away with the persistent tendency to eczematous outbreaks on the senile leg. How often have I laughed as a patient told me of his "gouty diathesis" diagnosis, when less soap and more grease, or an attack on the ringworm between his toes, gave him relief. But years of observation have only strengthened my appreciation of the importance as an index of constitutional overload, of the appearance of an eczema after the age of forty-five.

Every medico has his hobby; mine, I frankly confess, is the neurogenous factor in dermatoses, so that in presenting it to you, you will smilingly indulge a little enthusiasm on my part. Yet it is interesting to see how the horizon is widening in this direction among dermatologists. A state of mind, acting through the vasomotor system, and the as yet unknown mechanism of itching, *can* underlie the appearance of a dermatitis and nothing will finally avail to control it until the mind is set at rest. It is true, that there is usually an exciting cause identifiable, but it is so far nonspecific that at one time it may appear to be one thing, and at another, a different thing. A woman, worried with good cause about her husband's health, develops a dermatitis of the neck, of that type so familiar to me as a feature of my eastern transplantation that I call it "Philadelphia neck." Ingenious devices to protect the neck from irritants fail, and a full schedule of sensitization tests reveals that squirrel fur is the alleged exciting cause. The squirrel

coat is put away; the neck clears up. Two months later, when the worry has again become acute, the trouble reappears, this time without the intermediation of squirrel. The same picture develops time and again in women quarrelling with daughters who stay out too late; in women traveling wildly to escape the boredom of an old age with duties but no interests; in women, the ambitious wives of unambitious, retiring and scholarly husbands; in women with flower gardens but also with husbands forty years too old; in women who recover and yet keep their gardens, when their philosophy of life has triumphed over the seeming *impasse*. Just as Bloch has shown that it is possible to remove warts by psychotherapy and nothing else, so it may some day be shown by some sufficiently bold explorer, that it is possible to remove some forms of eczema by the same means. Today, however, I only claim that the mind and the nervous system provide the source and the transmitting mechanism for a powerful group of predisposing causes in the etiology of eczema.

Just how the nervous system acts in the production of these effects is a difficult problem. Hazen and Klauder were the first in this country to publish their impressions and researches, and there is a rapid accumulation of material in the last few years in the German literature, which centers around the vagus-sympathetic system as the probable reaction mechanism, and the calcium potassium balance of the skin as a fundamental chemical fact in the production of cutaneous irritability. No doubt, too, the gastrointestinal tract, whose susceptibility to emotion has recently been so beautifully summarized by Alvarez, is an important link in the sequence of events. The present status of knowledge is hardly much better defined than is that of the endocrin system, but the practical utility of calcium therapy and atropin suggests that there is some fire underlying all the smoke. There is not as yet any simple classification of all dermatoneurotics as either vagotonic or sympathicotonic, for it appears, according to Brill, that they may be either, and that they may be one thing with respect to their skins and another with respect to other groups of structures. In practice, however, it is usually easy to recognize the vagotonic, and he is the one, rather than the sympathicotonic, whom it is possible to help. The dermatoneurotic is not at all the nervous or outwardly emotional individual who finds relief in tears and screams. Such persons "blow off" and are relieved. The dermatoneurotic is controlled. His makeup, his "poker face" is perfect. He is the pillar of strength to whom all his friends and people come with their troubles. In storm he is calm, the master of every consciously controllable reflex, who never blanches before the blast. But for that perfect front, he pays, as I tell my patients, by an almost invincible predilection for "hollering down his backstairs." He sends outrageous, disturbing and contradictory messages to his sympathetic engine-room coördinating mechanism, by way of his

vagus speaking tubes. His is the inward tempest, the strife and struggle kept from the world. A little atropin, a little calcium, a few talks, a little physiotherapy, much rest and he can be transformed for the time being. Really to cure him may be the reëducational task of months.

Just how one recognizes the psychoneurotic background in the patient with a dermatitis it is a little difficult to say. There is an element of instinct in it, an appraisal of the small signs of tension that is done in part by the subconscious mind of the examiner. The vagotonic picture, or, perhaps, better, the disturbed vagus-sympathetic picture, is not hard to identify—the florid or flushing face; the moist, cold, perspiring, though red or bluish hands, the bright red line, or even wheal, that quickly follows a sharp stroking of the skin with a blunt implement (strich reaction). On this background, not alone urticarias and eczemas, but the dermatomycoses, thrive.

I see that I have read off the larger part of my page allotment without touching on the one most fascinating mystery, the one most intractable problem, and the one still *simon-pure* example of etiologically-defined constitutional eczema in the calendar. This is the eczema of the asthma-hay-fever complex, the so-called late eczematoïd of Rost or prurigo of Besnier. The clinical picture is distinctive in the large majority of cases. Involvement of the face, especially the forehead and the skin about the mouth and chin, and of the flexures of the elbows and the popliteal spaces, by a dry, thickened, leathery dermatitis, excoriated by scratch, is highly characteristic. Bursting from time to time, without apparent excuse, into exacerbations which may convert the face into a shapeless and oozing mass with slits for eyes and mouth, and a “blob” nose; the scalp hair gummed with sticky exudate of a pallid, sickening, sweetish odor, the ears swollen and dripping, the neck fissured, the arms and the legs furiously itching and torn—the disease is one to terrify victim and onlooker alike. When the fundamental incurability of the process is taken into account, together with its hereditary background and its ability to injure personal appearance, which is the source of so much that is necessary in livelihood and essential in the happiness of life, you can easily understand why I rate diathetic eczema as one of the crippling ailments that affect mankind.

In the background lies always a certain group of perhaps etiologically important facts: (1) An inherited tissue irritability, an atopy as the students of sensitization phenomena call it, which makes the patient abnormally susceptible to irritants, or rather, makes substances irritants for him, or certain parts of him, that are not irritants for the normal individual; in some way his cellular constitution is at fault. (2) The group of predisposing causes already discussed as active in the simpler eczemas—the ichthyotic

and the seborrheic makeup, the focal infections, the gastrointestinal dysfunctions and the metabolic abnormalities. (3) Overshadowing in its fundamental character all the others is, in the opinion of recent writers, an abnormal nervous system. Just what makes these patients a distinctive nervous group is again hard to define. Yet their reactions are startlingly alike. In all there is an inward tension. There appears over and over the "electric relation" between parent and child. The youngsters are violently, almost unbalancedly active. They quickly get out of harmony with the established order and are vigorously "don't-ed" back into line. They are precocious often. As they grow older, they become destinationists, as I call them, rushing always upon an end, with that, and not the road, in view. The commonplaces of psychiatry, sex substitutions and fixations may be implanted upon this soil as on any psychotic background, facilitated by the sense of inferiority that life-long helplessness in the face of such an ailment brings about. Multiple sensitivity to proteins with which the patient may or may not have contacts is a recognized commonplace in such cases and is the despair of one who seeks in skin tests a clue to extrinsic etiology. There is some distinctive response in the few, none in the many cases, and the results of a general medical workup are equally disappointing.

The notion that blood chemistry will reveal much worth while is questionable, for the intimate chemistry of the skin is more probably the site of the disturbance, if any. There is no reaction to ingestion of urates (Michael). The acid-base equilibrium is disturbed. (Dromet and Verain.) The sugar-chlorid ratio changes, the sugar tolerance drops (Usher and Rabinowitz); the precipitable calcium decreases (Burgess), the calcium-potassium balance is disturbed with a rise in calcium on recovery from an attack, and the reverse during an exacerbation. An attempt is being made, as yet unevaluated, to attach most eczemas to the trail of arsenic, unwittingly ingested in a multitude of ways. Endogenous toxins from the intestine are blamed likewise. As Nathan and Stern assert, all these are probably but epiphenomena, and not centrally significant causative facts.

Summary of Treatment of Eczema. How shall we treat eczema? If I were asked, as I am, to give in a closing paragraph a scaling ladder to the outer confines of an unconquered citadel, I should say:

1. Search for the external excitant, though it may be difficult to find and its removal may avail little.

2. Reduce the carbohydrate intake. Take a meal-by-meal history of the diet.

3. Know and grease the ichthyotic.

4. Look for dermatophytosis of fingers, toes and groins and for pustules. Your patient's eczema may be an infection.

5. Try to restore balance by correcting the outstanding errors in focal infection and gastrointestinal troubles.

6. Expect less of sensitization tests, metabolism determinations, blood chemistry and routine physical and laboratory workups, and more from a full history, an experienced appraisal of type and quasi-empirical management.

7. Keep water and soap away, and learn to juggle ichthyol and tars, especially crude coal tar.

8. Use Roentgen ray sparingly, the quartz lamp often, auto-hemotherapy oftener, calcium in large doses on an empty stomach oftenest.

9. Study the nervous background, but do not fall back on its explanations until the physical person has been completely searched.

10. Pray—for we must, in this wilderness, as Ochsner from the depth of a vast surgical experience said, “leave something to God.”

A CLINICAL STUDY OF MENINGOCOCCUS MENINGITIS.

AN ANALYSIS OF 190 CASES OBSERVED IN A PERIOD OF EIGHTEEN MONTHS.

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EPIDEMIC or meningococcus meningitis is a relatively uncommon disease which occurs both endemically and epidemically and is the main form of meningitis that occurs in epidemics. The only other type that may assume epidemic proportions is the pneumococcic form of the disease.

Epidemiologically this disease resembles poliomyelitis very closely as both are only mildly contagious. In an analysis of 500 cases of epidemic meningitis in New York, it was found by Neal that there were only 13 instances of more than one case in a household. This accords closely with the incidence in this series of 190 cases in which 5 instances of multiple cases were noted.

Epidemics seem to appear in cycles and in New York City these have been noted to occur about every nine to twelve years. This corresponds very well to our own experience in an analysis of cases that have been admitted to the contagious department of the Cook County Hospital.

In 1919, 43 patients with epidemic meningitis were admitted and in the succeeding years to and including 1926, the number of admissions was 16, 17, 9, 10, 9, 6 and 10, respectively.

This series consists of 190 consecutive cases admitted to the Cook County Hospital on the services of Hoyne, Bower and myself, from April, 1927 to September, 1928. Of the 190 cases, 132 (69.5 per cent) occurred in males, this being similar to the preponderance in the male of poliomyelitis and epidemic encephalitis. The youngest patient was three months of age and the oldest sixty-two years. There were 94 patients under fourteen years of age. It was thought best to include adults in this series for they constitute about a half of the patients and the symptomatology and therapy is practically the same as in children except for those under one year of age.

Headache, vomiting and fever were universal symptoms and rigid neck, Kernig and Brudzinski signs were found in every case except in infants under one year of age. Headache was not determinable in these cases and rigid neck, Kernig and Brudzinski signs were variable. Rigid neck was never present to the degree it is found in older children and adults, but existed in about one-half of the cases merely as an increase in resistance to anterior flexion of the head. In the other half of the cases in young infants, no rigidity was noted. Negative Kernig and Brudzinski signs were recorded in only 9 cases, all of whom were patients from three to twenty months of age.

Bulging fontanelle was observed in every case in infants whose fontanelles were still open.

The significance of positive cases of epidemic meningitis in infants with absence of the pathognomonic signs of rigid neck, Kernig and Brudzinski signs is apparent and the unreliability of these signs is of extreme importance in dealing with young infants who have symptoms or findings at all suggestive of meningitis. Spinal puncture should be resorted to in any suspicious case even though the meningeal picture is not complete.

Convulsions were present in 12 cases (6.5 per cent), 6 of these being in patients under two years of age and the others in children four to eight years of age, except for one case which occurred in a boy, eighteen years of age. Those with convulsions ended fatally in 58 per cent of the cases in which they were observed.

Cases with petechiæ are considered the most severely toxic variety. Petechiæ were noted in 28, (6.7 per cent) of the patients and the mortality in these cases was 64 per cent, which was only 14 per cent greater than the general death rate (Table I).

Herpes labialis occurred in 19 cases (10 per cent) and was most frequent in the recovered cases. The observation that herpes frequently made its appearance several days after treatment had been instituted is undoubtedly the explanation for its frequency of occurrence in the cases that subsequently recovered, for many of the fatal cases might have developed herpes if they had lived long enough. Strabismus was present in 24 cases (12.5 per cent) and was

a slightly more common finding in the cases that ultimately recovered than in those that proved fatal.

TABLE I.—MORTALITY WITH REFERENCE TO SYMPTOMS AND COMPLICATIONS.

Symptoms and complications.	No. of cases.	Recovered.	Died.	Mortality, per cent.
Coma	39	12	27	69.1
Semicoma, stupor, drowsiness	29	19	10	34.5
Delirium	33	20	13	43.2
Convulsions	12	5	7	58.3
Petechiæ	28	10	18	64.2
Herpes	19	12	7	36.8
Chills	20	11	9	45.0
Strabismus	24	14	10	41.6
Ptosis	4	2	2	50.0
Unequal pupils	3	2	1	33.3
Nystagmus	7	6	1	14.0
Unilateral deafness	2	2	0	0.0
Bilateral deafness	8	8	0	0.0
Suppurative otitis	4	2	2	50.0
Arthritis	7	6	1	14.0
Iritis	1	1	0	0.0
Chorioretinitis	1	0	1	100.0
Encephalitis	1	1	0	0.0
Panophthalmitis	1	1	0	0.0

Ptosis was observed in only 4 cases, unequal pupils in 3, nystagmus in 6 cases.

Deafness was the outstanding sequela. It was recorded in only 10 cases (1.9 per cent); however, this number was considerably increased on reëxamination months after discharge from the hospital. The type of deafness was that of complete loss of hearing due to nerve involvement and in a few cases was noted at the onset of the infection while in others it manifested itself during the course of the disease. Recovery or even slight improvement in hearing was never noted after the deafness had once developed. In our records 8 cases were recorded as bilateral and 2 as unilateral before discharge from the hospital. None of these patients died. This observation was due undoubtedly to the fact that these patients were under observation longer and had a longer period than the fatal cases to develop this complication.

In only 4 cases was suppurative otitis media noted as a complication, 2 in patients who recovered and 2 in fatal cases.

One patient developed iritis, 1 chorioretinitis, 1 panophthalmitis, and 1 encephalitis in the convalescence from the meningitis in a case that ultimately recovered.

Patients with extreme opisthotonos in most instances had a clear mentality, because of the greater localization of the exudate at the base of the brain. These cases showed a prompt response to serum therapy and the prognosis was good.

The average stay in the hospital of the recovered patients was 19.6 days, the shortest period six days and the longest sixty-five days. The greatest number of patients, 22, or 23.6 per cent of the total, were discharged from the hospital on the fourteenth and fifteenth days (Table II).

TABLE II.—STAY IN HOSPITAL OF RECOVERED CASES.

Weeks . . .	1	2	3	4	5	6	7	9
No. of cases	2	35	30	11	8	6	3	1

The mortality during the small epidemic of 1919 was 37 per cent and in the succeeding years 47 per cent.

The mortality in this series was 48.9 per cent. The epidemic began in April, 1927, when 14 patients were admitted, followed by a similar number in May, 12 in June and 5 or 6 in the months that followed. The mortality was highest under one year and over fifty years of age where it reached 87.5 per cent and 100 per cent respectively. The lowest mortality was noted between ten and twelve years of age where no deaths occurred. The youngest recovered case was that of a patient nine months of age and the oldest fifty years (Table III)..

TABLE III.—MORTALITY ACCORDING TO AGE.*

Age in years.	No. of cases.	Recoy-ered.	Died.	Mortality, per cent.
Under 1	8	1	7	87.5
1 to 2	12	5	7	58.3
2 to 3	4	3	1	25.0
3 to 4	18	15	3	16.6
4 to 5	6	4	2	33.3
5 to 6	6	3	3	50.0
6 to 7	5	1	4	80.0
7 to 8	9	6	3	33.3
8 to 9	2	1	1	50.0
9 to 10	6	5	1	20.0
10 to 11	5	5	0	0.0
11 to 12	3	3	0	0.0
12 to 13	4	2	2	50.0
13 to 14	4	2	2	50.0
14 to 20	39	24	15	38.2
20 to 30	25	11	14	56.0
30 to 40	13	4	9	69.2
40 to 50	13	2	11	84.5
50 to 60	7	0	7	100.0
60 to 62	1	0	1	100.0
Total	190	97	93	48.9

* The mortality is the lowest between the ages of 3 and 4, and from 9 to 12 years.

The mortality with relation to the state of consciousness on admission is a very important consideration since it may serve as an index of the prognosis. It was found that patients who were brought to the hospital in coma had a much smaller chance of recovery than those designated as semicomatose, stuporous or drowsy.

It was interesting to note that the duration of illness before admission was not as important a factor as is ordinarily believed. The patients who received treatment before the end of the first week of illness had a much better chance for recovery, however, than those who were ill seven days or more before treatment was instituted (Table IV).

TABLE IV.—MORTALITY ACCORDING TO THE DAY OF ILLNESS ON ADMISSION.

Day of illness on admission.	No. of cases.	Recovery.	Death.	Mortality, per cent.
First	20	12	8	40
Second	29	14	15	51
Third	30	20	10	33
Fourth	24	16	8	33
Fifth	4	3	1	25
Sixth	4	3	1	25
Seventh	8	3	5	63
Eighth	1	0	1	100
Twelfth	1	0	1	100
Fourteenth	3	1	2	66
Twenty-first	1	0	1	100

Failure to find organisms in a spinal fluid cloudy because of meningitis has been considered as circumstantial evidence in favor of the diagnosis of meningococcus meningitis. This was not well borne out by our observations, for in only 13 (6.76 per cent) were no organisms found. True, the meningococcus is not as abundant in a purulent spinal fluid as the streptococcus, staphylococcus or pneumococcus, but on careful search only in a few cases will one be unable to discover both intracellular and extracellular Gram-negative diplococci in material obtained by the first spinal puncture in a case of meningococcus meningitis. The picture is considerably altered as to the finding of organisms and the cell count after even one intrathecal injection of antimeningococcus serum.

The average cell count in the cerebrospinal fluid on admission was 11,780. The lowest count was 980 and the highest 90,000, in every instance showing a very definite polymorphonucleosis ranging from 75 to 96 per cent.

The fluid was cloudy on first examination in every case, but varied in degree from faint cloudiness to thickly purulent material that scarcely ran through the needle.

The globulin tests were universally positive.

The blood showed a leukocytosis in every case in which it was examined, the average being 23,700. The lowest white blood cell count was 11,200 and the highest 40,000.

Antimeningococcus serum of the polyvalent variety was used in the treatment of these cases. No difference was found in the therapeutic value of any of the brands employed, except that in a few instances definite improvement was not apparent until a change was made from one brand to another.

This brings up the question of how a more accurate and more scientific method of treatment could be established in this very serious disease. True, polyvalent serum is considered effective in the agglutination of all strains of meningococci, but it is reasonable to suppose that its efficacy may be more marked for one strain than another and the individual packages may also vary. A fresh serum may be more agglutinative for a particular strain than an older product. For this reason it is suggested that in the choice of a serum for a given case the agglutinating power be tested with the strain of organism causing the infection so as to employ the most specific serum. I hope to make this the subject of a report in the near future.

The average amount of serum used in recovered cases was 162 cc. intrathecally. The smallest amount in a case that recovered was 15 cc. intraspinally in two administrations and 15 cc. intravenously. The largest amount used was 495 cc. In 8 instances 50 cc. or less was sufficient to effect a cure.

Treatment consisted of the intraspinal injection of antimeningococcus serum immediately on admission and daily administration until the fluid became clear with a diminution of the cell count to a few hundred. With the improvement in the spinal fluid the clinical picture with relation to the meningeal findings improved and intrathecal injections were stopped. Daily spinal puncture drainage was continued, however, until the pressure returned to normal and the cell count returned to 100 or less. No serum was injected into these patients unless there was evidence of a recurring meningitis such as a reclouding of the spinal fluid or rigidity of the neck, Kernig or Brudzinski signs.

The largest amount of serum administered to a patient who died was 495 cc. given over a period of eighteen days with 15 cc. intravenously. This case was complicated by a preëxisting diabetes in a patient, aged forty-two years, who also showed a marked petechial rash.

Intravenous serum was administered to 68 patients, 39 of whom recovered, a mortality of 57.3 per cent, which is considerably higher than in the cases that were treated intrathecally only. The cases for intravenous therapy were chosen at random, this phase of the treatment depending mainly on the intern who first saw the

patient. The first intravenous serum injection was given at the time of the first intraspinal injection and subsequent injections were given at daily intervals along with the intrathecal injections. One dose of intravenous serum, 15 cc., was administered to 11 of the recovered cases, two doses to 11, three doses to 7, four doses to 2, five doses to 2, six doses to 3, ten doses to 1, and twelve doses to 2 (Table V).

TABLE V.—INTRAVENOUS THERAPY IN RECOVERED CASES.

Number of injections . . .	1	2	3	4	5	6	10	12
Number of cases . . .	11	11	7	2	2	3	1	2

The average number of spinal punctures in the recovered cases was 8.1. The smallest number was 2 and the greatest number 30. The greatest number of spinal punctures in a case that finally succumbed was 20.

Complications after or attributable to spinal punctures consisted only of the appearance of chills followed by collapse in 6 cases, in 5 of which intravenous-serum therapy had previously been used.

Serum rash, which made its appearance from the seventh to the twelfth day, was present in 26 cases, in 17 of which intravenous-serum therapy had been used. This reaction occurred equally in the recovered and the fatal cases. One patient developed a severe serum reaction on the twenty-eighth day after treatment was instituted. This patient was first given intravenous serum on the seventh day and received in all 135 cc. intravenously.

Cisterna punctures were performed in 12 instances. This procedure was resorted to only if the opisthotonus was so marked that sufficient flexion of the back was not possible to permit of spinal puncture, or if sufficient fluid was not obtainable by spinal puncture due to obstruction in the spinal canal by organization of the exudate. Four of these 12 patients recovered after two or three cisterna punctures.

The average cell count of the spinal fluid obtained two to five days before discharge from the hospital was 49 cells per c.mm. In no instance was the cell count found to be below 12. The type of cells was not noted.

The follow-up on these cases consisted of the reëxamination of 61 of the recovered patients from two to sixteen months after discharge from the hospital. The remaining 35 patients we were unable to locate.

Of the 61 patients, 34 (55.7 per cent) were entirely free from complaints and in many instances told of feeling much better than before the onset of the illness. In this number there were two children whose mothers reported an improved mental condition since the illness.

The outstanding sequela was deafness, which occurred in 16 (25.4 per cent). Twelve of these patients had a bilateral total deafness while the other 4 had complete loss of hearing in only one ear. In 2 instances the deafness did not make its appearance until two and a half and three months, respectively, after discharge from the hospital. Both of these were bilateral cases and the patients had normal hearing on discharge from the hospital. This could be explained only by scar-tissue contraction about the eighth nerve resulting in atrophic nerve changes.

Lumbar pain was the next most frequent complaint and occurred in 8 cases (13 per cent). It was generally described as an occasional pain at the site of the lumbar punctures, but 2 patients complained of severe, agonizing pain on bending the trunk forward.

Next in frequency was vertigo, which was complained of in 5 cases; 4 of the patients described it as slight while one told of marked dizziness followed by falling, but never accompanied by loss of consciousness.

Generalized weakness was noted in 3 cases, and described as a tired feeling and indisposition to be as active as previously.

Aching of the legs was complained of by 3 patients, all of whom also experienced lumbar pain.

There was one case of impaired mentality in which the mother noted the child's inability to learn at school.

One patient developed swelling of the left leg which disappeared on rest in bed and recurred on the resumption of the upright position. This was apparently due to thrombosis of the large veins.

Only one patient complained of headaches, which were not very severe and occurred only occasionally.

Strabismus was noted in only one case although it was observed in 14 recovered cases during the patients' stay in the hospital. This shows a marked tendency for improvement in eye complications.

One patient complained of anorexia while 3 told of an increase in appetite.

One case is worthy of special mention because of the very unusual sequences of events in the course of the illness.

Case Report. In March, 1928, the patient, a woman, aged twenty-two years, entered the hospital with a typical case of epidemic meningitis that responded in the usual manner to serum therapy. The patient left the hospital in good condition sixteen days after admission. Two weeks later she returned to the hospital with the complaints of headache, dizziness and vomiting. There was no neck rigidity, Kernig or Brudzinski signs. The vomiting was severe and responded only to a very rigid dry diet. The diagnosis made at that time was postmeningitis cerebral irritation and starvation acidosis. No spinal punctures were done at that time and the patient recovered except for a slight dizziness and left the hospital in six days.

Eight months later she again entered the hospital with the complaint that for several days she had had a "head cold" and for the past two days severe headache and vomiting with dizzy spells and generalized aching. At this time there was only slight rigidity of the neck and the Kernig and Brudzinski signs were negative. Spinal puncture was performed and cloudy fluid under increased pressure was obtained. Meningococci were discovered in the smear and there were 15,000 white cells per c.mm.

On the second day the patient showed marked rigidity of the neck with a positive Kernig and Brudzinski sign and only 5 cc. of fluid was obtainable on spinal puncture, but 35 cc. was obtained on cisterna puncture. Cisterna puncture was then performed daily for the next four days with the introduction of 30 cc. of antimeningococcus serum and the patient left the hospital cured in nineteen days.

Just what lesions existed during the eight-month interval is mere conjecture but the first return to the hospital spoke for some cerebral irritation and the only possibility for a focus to remain quiescent and then be reactivated after eight months would be for it to have been localized somewhere in the spinal canal, as in the cervical region. The failure to obtain much fluid on spinal puncture would speak for a partial block in the spinal canal below the cisterna magna.

Then again one cannot exclude the possibility of a reinfection, but the return of the symptoms of headache and vomiting two weeks after the patient's first discharge from the hospital leads one to believe that the meningeal process was active at that time.

The absence of meningeal symptoms on the first examination during the second attack would speak for a localized spinal meningitis and dissemination to the cerebrospinal meningitis after intrathecal serum administration.

Summary. A report is made on 190 cases of meningococcus meningitis observed in a period of eighteen months at the Contagious Division of the Cook County Hospital.

The analysis includes a report of multiple cases in one family, the average stay in the hospital of recovered cases, the age frequency, the mortality according to age, the clinical picture, the day of illness that treatment was instituted and the type and rationale of treatment employed, the complications with relation to their frequency and prognostic value, the spinal-fluid findings, the cisterna-puncture results, and the reports of reexaminations made months after the patient's discharge from the hospital. The occurrence of deafness two and a half and three months after discharge from the hospital deserves special emphasis. Finally, the absence of meningeal symptoms in infants and the apparent futility of intravenous serum therapy are noted.

THE LARGE BOWEL IN CHRONIC ARTHRITIS.*

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THIS communication has to do with the incidence of the abnormal variations in shape and size of the colon in chronic arthritis and the changes which may take place while the patient is under dietetic treatment.

It is not a new observation that these disturbances occur in chronic arthritis, although they have been largely of surgical interest. Goldthwaite and Osgood pointed them out and, in treatment, applied various orthopedic measures. Lane associated arthritis with intestinal stasis, which he believed due to membranes or kinks. He and others reported improvement, and even cure, with colectomy and with plastic operations. However, due apparently to the general belief in the infectious etiology of arthritis, this aspect of the disease has received little attention.

These colon lesions may have another significance. In monkeys fed with autoclaved diets, McCarrison produced changes in the colon which he described as a "ballooning of the large bowel and a tissue-paper-like structure of the viscus." From his investigations on experimental animals, he concluded that atony of the human colon is the result of malnutrition.

It is well known that variations in diet and states of nutrition influence the course of chronic arthritis. For years Pemberton has insisted on this, and has treated many cases of arthritis with low-calorie diets, restricting carbohydrates especially. Some years ago we had occasion to stress the importance of balance in the diet between carbohydrate, protein and vitamins; others, notably Rowlands, associated the disease with vitamin deficiency.

In a series of 60 patients with chronic arthritis the large bowel has been examined by Roentgen ray following a barium enema, and changes which we considered abnormal were observed in 65 per

* Read before the meeting of the Association of American Physicians, Atlantic City, May, 1929.

cent of these cases. The Roentgen ray picture shows changes in tone, haustral markings and length. Atony is sometimes seen throughout the entire colon, or more frequently it is confined to the cecum where it may be extreme. Haustral markings, in the atonic areas, are usually absent or much decreased, and this decrease in haustration may extend throughout the large bowel. The length of the colon may be so increased as to result in change of shape or even extensive looping and redundancy.

This Roentgen ray picture has been studied from time to time while the patient has been on dietetic treatment, and it has been found that the colon assumes a more normal appearance. Most effective results have been observed with the use of diets high in vitamin and low in carbohydrate. The antineuritic vitamin has been given freely in the form of baker's yeast or wheat germ. As a rule, the calories were restricted to some extent.

The illustrations show how much change may take place. The tone of the cecum sometimes increases very much, and there is almost always well-marked increase in the depth and regularity of the haustral markings. Usually the colon becomes shorter; the looping and redundancy may disappear. The transverse colon becomes straighter, giving the colon, as a whole, an H-like appearance.

Many patients have been observed now for some months' time. In practically all improvement has been noted in the Roentgen ray appearance of the colon. This improvement may continue for several months' time while the patient is on a diet high in vitamin and low in carbohydrate. As a rule, the patients are much benefited by this dietetic treatment, sometimes very much so. Observations have been made on patients suffering from rheumatoid-arthritis and from osteoarthritis. On the whole, better clinical results have been noted in the rheumatoid group.

These observations are offered to support the belief that nutrition and chronic arthritis are related. Such a belief is not opposed to the general view that chronic arthritis is of infectious origin. Deficiently fed animals are highly liable to infection and infection may complicate or be part of a deficiency syndrome. In many of the cases studied focal infection was present. It may be that malnutrition creates a state favorable to the development of infection. In some cases the bowel itself may be the source of the infective or toxic agent causing the disease.

The value of carbohydrate restriction in arthritis may also be explained on these grounds. Carbohydrate favors the development of deficiency disease and with vitamin B restriction it is difficult to produce the deficiency disease unless carbohydrate is given in excess, as, for example, polished rice. In our clinical observations we have found carbohydrate reduction an important part of this dietary treatment.

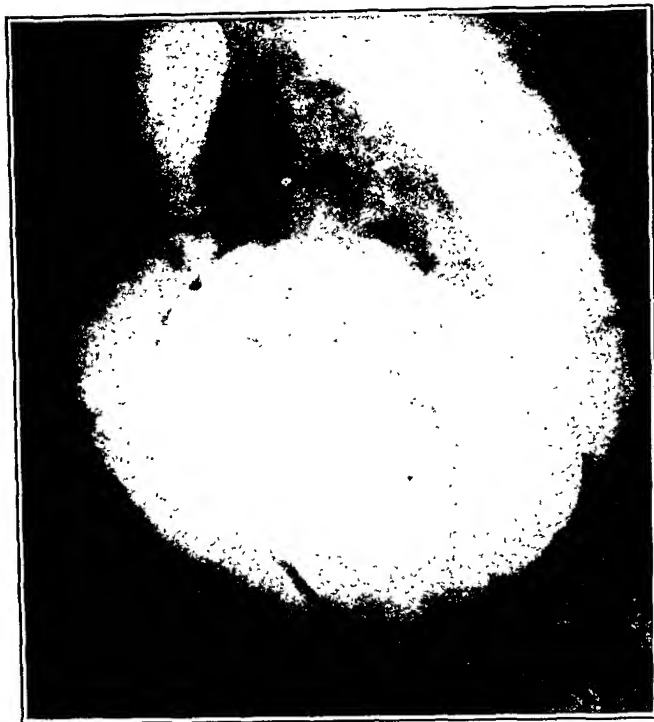


FIG. 1



FIG. 2

FIGS. 1 and 2.—Miss C., aged seventeen years. Pain and swelling of the metacarpal phalangeal joints for ten years. During the summer of 1928 arthritis developed in knees, ankles and shoulders. No history of sore throats, no focus of infection found. Admitted to hospital, September 29, 1928, showing moderately severe arthritis of rheumatoid type and also aortic and mitral valve lesions. Changes are shown which occurred in the colon over four weeks of dietetic treatment. Much clinical improvement observed while patient was under this treatment.



FIG. 3



FIG. 4

FIGS. 3 and 4.—D, aged forty-four years. Rheumatoid arthritis of one year's duration. History of obstinate constipation. No focus of infection found. Recovery while under dietetic treatment. Above changes in the colon took place over two months.



FIG. 5



FIG. 6

FIGS. 5 and 6.—Mrs. S., aged thirty-five years. Severe rheumatoid arthritis for four years. For many years has had a discharging middle ear. Above changes took place over one month of treatment with diet.



- Conclusions.** 1. It is believed that the abnormalities observed in the colon in arthritis are manifestations of malnutrition.
2. Malnutrition frequently plays a part in the development and course of chronic arthritis.
3. The abnormalities found in the colon are markedly improved by dietetic treatment with coincident improvement in the arthritis.

THE USE OF DEXTROSE IN PNEUMONIA.*

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It is our purpose to present some clinical observations which we have made during the past four years on the use of dextrose in the treatment of pneumonia. It is our belief that it is of value, but we also know from our observations that this procedure has definite limitations. Further, we are aware of the danger of suggesting another form of therapy, which we may regard as beneficial, in a disease such as pneumonia.

In any discussion of pneumonia, particularly in reference to therapy, it should be defined as clearly as possible as to whether the cases in question are toxic or nontoxic pneumonias. It is a common experience to observe both forms in almost any pneumonia service during the season when this disease is prevalent. They have an entirely different prognosis. Further, it is also important to know, when speaking of this disease, what is the usual mortality in the community: is there a great deal of pneumonia with a high death rate or are there very few cases and a low death rate? In such a community as the former, therapy in the toxic case is a great problem; while in the latter, treatment is a more simple matter. Pneumonias in children should not be considered with the adult form, nor do we include any postoperative pneumonia. In other

* Read by title, Association of American Physicians, Atlantic City, 1929.

words, in order to estimate the therapeutic value of any method of treatment, particularly in a disease such as pneumonia with its variable virulence, it is most important to judge the results from those cases which are toxic and likely potential fatalities, rather than from the mild forms which have a higher percentage of recovery. It is granted that one cannot always differentiate these forms, but we believe there are some definite points which can separate them fairly well. Nontoxic cases may later become toxic; in fact, the majority of pneumonia patients for the first three days are not obviously toxic. Naturally, there are exceptions as when toxicity is present almost from the onset of the infection. We see many of this character. In communities which have pneumonia with a high mortality, and particularly if such a condition has been almost a fixed problem in that it repeats itself year after year, there is a tendency to accept the mortality as unalterable and possibly become fatalistic in attitude, or certainly nihilistic, as far as therapy is concerned. On the other hand, the opposite attitude also occurs, for in what disease have we used more drugs than in pneumonia? Have we not had the opportunity year after year to observe the valuelessness of certain drugs in our fatal cases, and at the same time note the nontoxic case recover without any particular therapy? Such clinical observation has been common knowledge for many years.

Pneumonia has been a reportable disease in Pittsburgh for the past four years, averaging about 3300 cases yearly, with a mortality a little over 40 per cent. McMeans has reported the following percentages on the serologic types of the infection observed in Pittsburgh (2998 typings): Type I, 17; Type II, 14; Type III, 14; Type IV, 53. It is, therefore, obvious that the usefulness of serum is markedly diminished in view of the small number of Type I cases. Further, probably one-half of these cases are not admitted to the hospital until after the third day, thus adding another disadvantageous factor to the giving of serum. Type III and some of the Type IV cases appear to be the most virulent clinically. Robinson has noted this in our pneumonias and also has found that Type IV can be subdivided into a few groups. Cooper, Edwards and Rosenstein have recently written on the same subject with reference to the New York cases. They noted that Type IV contained a number of fixed subgroups. It is to be hoped that in the future an effective polyvalent serum may be available along the lines of Felton's serum as recently reported by Park and by Cecil. In the meantime other methods should be tried, and it is really for this reason we have been interested in the use of dextrose. At the present, as far as our own problem is concerned, there is no available specific drug or polyvalent serum.

Randolph has recently reported on certain features of pneumonia in Washington, D. C. He believes that *Streptococcus hemolyticus*

is the common etiologic factor in their clinical problem. The pneumonia in Pittsburgh is pneumococcic in most instances. We see *Streptococcus hemolyticus* in a certain number of the empyemas, but whether this indicates absolutely that the original infection (pneumonia) was also the same may be difficult to say, although it is likely that it is the same organism. We have never seen a blood culture in pneumonia showing *Streptococcus hemolyticus*. It is always pneumococcus, and blood culture findings are more accurate than those of the sputum. Possibly in streptococcic pneumonia a bacteremia is not common. Further, in our observations, in case an empyema developed in a patient who had had a positive pneumococcic blood culture, the organism was the same in the pus from the chest. We regard most of our pneumonias as bronchopneumonia and that much of the lobar distribution is a manifestation of a coalescing process. Is it not possible that the terms "lobar" and "broncho" have outlived some of their usefulness, and that we should think more in terms of toxic and nontoxic pneumonia? During the four-year period in which these cases were studied we have noted that our pneumonia has slightly changed with regard to its time of appearance. December, January and February were formerly our most active months, but in recent years, during March, April and May, most of the infection has occurred. Last year May showed the greatest mortality. We do not include in this the influenza epidemic of December, 1928, when a great deal of pneumonia was seen. It may also be stated that our pneumonia is present every month of the year, few cases, of course, in the summer, but often these cases carry a very high mortality.

In our treatment of pneumonia we have used what is generally regarded as the proper symptomatic procedures of therapy, from mustard plasters locally to the use of oxygen by the mask method. We have not had the opportunity of using the Barach tent. Naturally, with an infection of known high mortality, an ample opportunity to test out any method on toxic cases has been afforded. We have long since lost all faith in the effectiveness of digitalis and oxygen as life-saving measures in toxic pneumonia, although we know that the latter gives symptomatic relief and have seen isolated instances, very few in number, when it appeared to be life-saving. Symptomatic relief is not enough as a therapeutic test in a disease such as pneumonia, and symptomatic relief in nontoxic cases and toxic cases in the end is quite a different problem. We do not think the other details of treatment merit any particular mention, save to say that we regard pituitrin, atropin, morphin and occasionally caffein as of value, but we have never been impressed with alkalies, especially sodium bicarbonate. Moderate dosage of potassium citrate (30 grains, q.i.d.) we often use in a routine way. It is taken for granted that fluids are forced, and that nursing, perhaps the most important factor, is efficiently carried out from the onset of the disease.

As we have referred especially to toxicity, it might be well to attempt to give our criteria of such a state. Naturally, there is bound to be a personal factor involved for what is a toxic case to one may not be so to another. With this in mind we have tried to estimate this very important state of the patient from signs which we believe from experience to be reasonably certain. We realize, of course, that one can never be too sure of clinical signs, as different individuals may react in atypical ways. However, there are two points to which we wish to call attention. A pulse rate of 120 or over, not immediately following any movement or exertion in bed or any excitement, such as a physician coming into the room, that is constant at almost any stage of the illness usually means a toxic case in our pneumonias. This is especially true if it has been gradually rising and the closer it gets to 140 the more likely is the case to be a fatal one. In our judgment this is the most sensitive guide to toxicity in the pneumonias that we see in this community. The second factor is a positive blood culture. Pneumonia with a pneumococcus in the blood, irrespective of community, carries a very high mortality (Cecil, 78 per cent; Cole, 67 per cent; our first series, 73 per cent). We have seen occasions in the past where the usually virulent Type III appeared to be very mild, even in the presence of a positive blood culture. This, however, is only the isolated observation. The number of pneumococci in the blood, as pointed out some years ago by Sutton and Sevier, and later by many other observers, is probably of much importance, the greater the number of colonies the higher the death rate. Blood culture studies on pneumonia are very valuable, and during the past year we have, at times, repeated them to find an early negative and a later positive result. All toxic cases with a negative blood culture should have second cultures, if possible during the last twenty-four to forty-eight hours of their illness, as it is probable that a higher percentage of them will show a bacteremia. Richey and Goehring, in our laboratory, noted that in agonal blood cultures on patients dying from a pneumonia, terminal or otherwise, pneumococcus was found in 50 per cent. As some of these pneumonias were post-operative or terminal factors in chronic conditions, it may be that in pneumonia as a primary disease the number would show a higher percentage. From our own results the type of case upon which we wish to have more accurate information, we repeat, is the fatal one carrying a negative blood. Our figure of 32 per cent mortality for negative blood culture cases (see Chart IV) is very high, although our percentage of positive cultures, about one-third of the cases, agrees with the number reported elsewhere. In Cole's studies 343 cases of lobar pneumonia in which blood cultures were negative showed a death rate of only 11.6 per cent; while in 119 cases in which the blood cultures were positive the death rate was 67.1 per cent. Repetition of the blood culture as was done by Sutton and Sevier

will likely demonstrate that a certain number of negative cases will later be positive, particularly if they are toxic ones. By this method they showed in 43.8 per cent of their cases a positive blood at some stage of the disease. This has also been noted by others (Cole, Cecil, Irons), and we have as previously stated, made the same observation. In none of our cultures have we attempted to estimate quantitatively the pneumococcus present. This would add valuable information, even though it entails a good deal of extra work for a routine study.

The first report on the use of dextrose in pneumonia was by a French writer, Enriquez, in 1914. He gave a 25 per cent solution intravenously three or four times a day in 250-cc. amounts and reported that good results were observed. In this country in the same year Litchfield made a similar report, using dextrose in practically the same way as had Enriquez. Both of these writers believed that dextrose was of value as a food and as a stimulant to the heart. There were no further observations until the influenzal epidemic in 1918. At that time John, Wells and Blankenship, and Koons reported favorably on its use in pneumonia. Ten per cent solution given intravenously two or three times per day was the usual method employed by these writers. Two English workers, Bennett and Dodds, in 1925, gave from 200 to 500 gm. of dextrose by mouth in lemonade in each twenty-four-hour period and they believed it to be of value in the pneumonias which they studied. Bollman, Hummel, Prisbram, Pfalz, Hay, Stejskal, Johnston and Mitoldschey have also mentioned that dextrose is of value in pneumonia and in toxic conditions. The experimental studies of Edmunds and Cooper on the toxic myocardium showed that dextrose solution given intravenously had the power of restoring the heart beat when all other measures failed. It was this work that induced us to use dextrose in the toxic cases of pneumonia, and we were impressed with the results during the first year of trial. Most of the German literature has been in reference to the relation of dextrose to the heart following the work of Budingen, who believed that intravenous dextrose was of value in angina pectoris. Klewitz opposed this view, but Jagic and Klima, Meyer and Hess confirmed Budingen's work. These latter observers believed that the action of digitalis was improved following the use of dextrose. One of us (Lynch and Webster) has already reported a series of pneumonia cases in which the favorable effect of dextrose solution intravenously was noted as compared with control cases under digitalis therapy.

At the present time, in our opinion, the best way of giving dextrose in a case of pneumonia is as follows:

1. From 400 to 600 gm. of dextrose are given by mouth per day. The most practical method of accomplishing this is to dissolve 200 gm. of dextrose (Dextrose Powder—Corn Products Company) in 1000 cc. of water, to which is added the juice of 2 or 3 lemons.

The liter thus contains 800 calories. It is very palatable, and we try to have the patient drink from 2 to 3 liters each twenty-four hours (1600 to 2400 calories). It is given frequently in small quantities during the time the patient is awake. If too sweet for the patient add more water or regulate according to individual taste. All cases are treated this way from the earliest time possible in the disease. We have noted that pneumonia cases having private nurses have much less difficulty in taking over 2000 calories per day by this method than do the ward patients. Good nursing, therefore, is very important with reference to this particular phase of treatment; in fact, it is essential. At times, patients seem to be quite unable to take the dextrose lemonade on account of the nausea and vomiting which is occasionally seen early in the disease, and also after taking large amounts for several days the stomach becomes irritable and further ingestion is difficult. We have tried other vehicles for dextrose, but have not been very successful. Williams and Pfluke have informed us that they have had no difficulty in giving 2000 to almost 3000 calories per day of dextrose in this way.

2. When it is impossible to give dextrose by mouth in a sufficient amount or when the case appears to be toxic, a 25 per cent solution of dextrose is given intravenously four to six times each twenty-four hours. The quantity injected never exceeds 200 cc. at one time. It must be given slowly, at least one-half hour for the injection. We find that in very toxic cases it is often impossible to get the patient to drink any satisfactory quantity of the lemonade, hence the intravenous method is necessary. By this method from 800 to 1200 calories can be given daily, in addition to a similar number by mouth, if possible. It is most important that increasing toxicity, even when the patient is taking dextrose satisfactorily by mouth, be met in this way as early as possible. This measure is of no value in moribund cases. One may add that 50 per cent dextrose solution may be used intravenously.

According to our charts, we have divided the cases into two groups as regards dextrose treatment, namely, adequate and inadequate. This grouping is not always easy to define but we are attempting to reach some quantitative factor so that results can be more easily read. As with any drug or serum, a sufficient dosage is essential for therapeutic effect. Our present conception of adequate dextrose treatment is, at least, 400 gm. of dextrose by mouth per day, or when given intravenously, at least 200 gm. (50 gm. four times a day). It is the total caloric intake that counts, whether by mouth or vein, and the closer one gets to 2400 calories per day, the better.

We are inclined to feel that the main value in dextrose is in the additional freely available calories of carbohydrate, as was mentioned by Enriquez and Litchfield, and as Meakins has so well stated, "I am convinced that in pneumonia, for the prevention of

cardiac failure, it is essential to maintain the carbohydrate and glycogen reserves by the intake of relatively large amounts of glucose. This is accomplished by the administration of copious quantities of fluid and carbohydrate, intravenously, if necessary, early in the disease, and not when the patient is *in extremis*." According to DuBois, pneumonia is associated with a 20 to 50 per cent increase in metabolism. The 1200 to 2400 calories of food given by this method should, at least from the physiological point of view, be of value, and may be the deciding factor in recovery. It is a common observation to notice a better pulse after intravenous dextrose. Whether this is due to any direct action on the heart or not we do not know. Edmunds believed possibly there was a direct action on heart muscle; however, it may act indirectly by improving general nutrition, as suggested by Meakins. It is our impression that in a toxic case we see more improvement in the patient's condition from the same number of calories given intravenously than by mouth. We speak of pneumonia as being a self-limited disease, and if the patient is able to hold out for sufficient time, enough antibodies will be formed so that recovery takes place. Possibly dextrose acts entirely in helping the patient "go the distance," or, in other words, it supplies the individual with the nutrition with which to fight the infection. In the past nutrition has been a problem, as the toxic pneumonia cannot take food in a satisfactory amount. Milk and its preparations do not appear to be easily handled by the sick pneumonia patient. When solid and liquid food is taken freely and easily, in our experience it usually means a very mild infection, and these cases do not make up our high mortality lists. For this reason, in the recent past our teaching has been to give an abundance of water, but no solid, even if light food, to the toxic case. It is in this regard that dextrose is so valuable, a high caloric intake can be readily maintained without much difficulty. Erlanger and Woodyatt have shown clearly the pharmacologic action of dextrose and how much of it can be metabolized. There are certain practical advantages in the method here suggested. It is easily carried out, and, therefore, can be used readily by the practitioner at the onset of the disease. On the other hand, cases seen in hospital practice are often more advanced and intravenous therapy may be the only method possible to use. This procedure is not difficult to perform in a hospital, but it is quite difficult in private practice. We have not used the subcutaneous method of giving dextrose, although it is accepted that it is of value. We have always felt that it disturbed the patient too much. Dextrose by bowel is not of much value in this disease as the caloric intake is too small.

In the earlier years of this work, we now feel, dextrose was in the main incorrectly used. It was only given intravenously to the toxic cases, but now patients can take it by mouth at the onset of the

infection, and perchance, some of them who later would otherwise become seriously toxic may be saved from going into that state. It is a very difficult matter to be certain about this, as we have observed cases become very toxic when taking from the beginning a goodly number of calories by mouth. However, we feel that it is a good practice to follow and certainly on a physiologic basis. Further, in the past, we were inclined to wait too long or the patient was too long in a toxic state before giving intravenous dextrose. It must be given earlier, and it is useless when the patients are moribund. Also, we did not give dextrose frequently enough or in a sufficient strength. Twenty-five per cent four times a day is better than 10 per cent twice a day as was our former practice, and an intake of 600 gm. by mouth per day is better than 200 gm. per day. Early in its use we stopped giving larger amounts than 200 cc. intravenously, as we observed evidences of reactions and circulatory embarrassment with larger quantities as Clark, Robertson, Oliensis and Stern had noted. Venous pressure records were made in cases receiving intravenous dextrose solution, using the instrument and technique of Hooker and Eyster. The venous pressure was used to detect circulatory embarrassment which might result from the addition of fluids to the right side of the heart. An increase in pressure above normal was an indication to reduce the amount of fluid given per dose. Frequently venesection was resorted to before giving dextrose intravenously in cases with an increased venous pressure. By this method the danger of producing circulatory failure by intravenous injection is minimized. This work will be reported separately by one of us. Chills have been noted after the injection at times. Since we have put one person in entire charge of the preparation of the solution, the reactions have been reduced to a minimum. In patients beyond middle life we have occasionally seen a reaction which seemed to be harmful, and in this type of patient care should be taken against a repetition, because if a second reaction occurs we do not continue the intravenous method of therapy.

The clinical improvement we have noticed in the cases that respond is definite. The pulse is stronger and slower, and the patient looks less toxic. We would emphasize, however, the pulse rate as the most important guide as to prognosis. We are not overly impressed by the importance of blood-pressure readings, although it is generally admitted that a falling pressure is not a good sign, but a normally low pressure even under 100 may be quite compatible with a mild or toxic pneumonia and recovery. Newburg and Minot, some years ago, referred to this, and we agree with them. In our opinion, the blood pressure is undoubtedly of less value than the pulse rate as an index of prognosis. The white cell count rises as improvement occurs, unless the count was a high one at the beginning. We have at times seen a count of 4000 to 6000 increase

to 20,000 in two days, and frequently observed lesser rises. Sugar may appear in the urine in small amounts, but when the administration of dextrose is properly spaced this can be avoided.

CHART I.—1925 TO 1928.

Mortality of Cases Treated with and without Dextrose.

	No. of cases.	Mortality percentage.
Dextrose treated	74	60.8
No dextrose	86	27.9
Total	160	43.1

During this period only the more toxic cases were treated with dextrose, and in nearly all the intravenous method only was used. Further, it was rarely given more than three times daily. Very few of the above cases we would now consider as having been adequately treated.

CHART II.—1925 TO 1928.

Analysis of Mortality in Dextrose-treated Cases. (74 Cases with 60.8 Per Cent Mortality.)

1. 48.8 per cent had one day of treatment
2. 22.4 per cent had two days of treatment.

71.2 per cent had not more than two days' treatment.

This group of fatal cases included many that were moribund or treated late in the disease. Almost three-quarters of the cases received less than three days of treatment. This is due to the fact that only the more toxic patients were treated, and frequently the beginning of treatment was too long delayed. The intravenous method only was in use over the greater part of this period, and represented much smaller amounts of dextrose (in grams) than we now use.

The high mortality in the positive blood culture cases is to be noted, also the relatively high percentage in the negative cases. There is nothing to indicate a favorable action of dextrose in this chart.

We would call attention to the comparison between the mortality in the positive blood-culture cases in Charts III and IV, and also to the difference between the adequate and inadequate treatment results in Chart IV. Moribund patients are included in all charts, and this probably accounts for the very high mortality percentage in the positive blood-culture group with inadequate treatment. The cases without blood cultures are merely included to indicate the severe form of infection that we see, many being in the hospital only for a short period of time. The age mortality agrees with the observations of Fergusson and Lovell who have recently studied the pneumonia in Manchester, England. It is possible that the high mortality in the negative blood culture cases is an index of the severity of the pneumonia in this community.

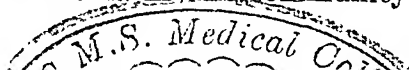


CHART III.—1925 TO 1928.

Pneumonia Mortality in Relation to Blood Cultures.

Blood cultures taken	72
Blood cultures positive	19 (26.3 per cent)
Blood cultures negative	53 (73.7 per cent)

Mortality in Positive Blood Cultures.

	Cases.	Per cent.
Died	14	73.7 (12 had dextrose)
Recovered	5	26.3 (2 had dextrose)
Total	19	

Mortality in Negative Blood Cultures.

	Cases.	Per cent.
Died	16	30.2 (12 had dextrose)
Recovered	37	69.8 (16 had dextrose)
Total	53	

CHART IV.—1928 TO 1929.

Pneumonia Mortality in Relation to Blood Cultures.

	Number.
Cases	126
Deaths	53
Mortality	42 per cent
Blood cultures taken	97
Positive blood cultures	29 (29.7 per cent)
Negative blood cultures	68 (70.3 per cent)
Cases without blood cultures	29

Mortality Percentages.

	Per cent.
Patients with positive blood cultures:	
29 with 15 deaths	51.7
17 with adequate dextrose, 5 deaths	29.4
12 with inadequate or no dextrose, 10 deaths	83.3
Patients with negative blood cultures:	
68 with 22 deaths	32.3
43 with adequate dextrose, 8 deaths	18.6
25 with inadequate or no dextrose, 14 deaths	56.0
No blood culture taken:	
29 patients with 16 deaths	55.1
3 patients with adequate dextrose, 1 death	33.3
26 patients with inadequate or no dextrose, 15 deaths	57.6
Mortality with reference to age:	
Cases under forty years (55 per cent)—mortality	20.0
Cases over forty years (45 per cent)—mortality	64.0

Summary. In the treatment of pneumonia, particularly of the toxic forms, we have described a method whereby it is possible to maintain a high caloric intake of food in the form of dextrose lemonade by mouth and hypertonic (25 per cent) dextrose solution intravenously: 2400 calories per day may be given. The nutritional value would appear to be the most important factor in this form of therapy, but there are clinical signs of an improved circulation after the intravenous therapy which might indicate a direct action on the heart muscle. The method of treatment is a physiologic one, and in the advent of an effective available polyvalent serum may still

be of value as a supporting measure in treatment. This form of therapy has previously been described, but for some reason has been discontinued. From our limited experience stated above, we would recommend a further trial of this method, and would suggest that its value be estimated from the results seen in those pneumonia cases which have a bacteremia, and which are given an adequate therapeutic test.

In our first series of 160 cases for 1925 to 1928, as indicated in Charts I, II and III, dextrose was given only in small amounts intravenously and only to the toxic cases. This accounts, we believe, for the marked difference in the result as seen in our second series 1928-1929 of 126 cases which occurred in a year when the general mortality was the same. In the second series, dextrose was given much earlier in the disease and in larger quantities both by mouth and by vein when necessary.

Positive blood-culture cases in the second series showed a 22 per cent lower mortality than in the first series. Moreover, the number of cases in the second series was larger.

There is a definite lowering of mortality as seen in Chart IV in all groups of cases which received adequate dextrose treatment.

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THE PATHOGENESIS AND TRANSMISSION OF TUBERCULOSIS.*

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WE are, I believe, gradually acquiring a conception of tuberculosis that explains many obscure aspects of its pathogenesis and promises to modify profoundly procedures for its control. Briefly stated it is that tuberculosis of early life has the characters of a first infection, whereas tuberculosis of later life is a disease modified by acquired immunity. This conception though obviously not new is just beginning to find its way into textbooks of medicine and pathology and has had almost no influence upon measures directed to combat the disease, which have remained practically unchanged since the era when knowledge of Koch's discovery of the tubercle bacillus became widely disseminated.

For at least two decades we have known that nature has somewhat inefficiently accomplished for tuberculosis that method of protective inoculation that has been the most successful means of combating infectious disease. Smallpox has been largely overcome and typhoid fever is demonstrably controllable by protective inoculation. We know very well that few children in the large cities of America and Europe escape inoculation with tuberculosis before they reach adult life. Anatomic demonstration of the scars of healed tuberculous lesions and observations made by testing children with tuberculin have furnished convincing evidence that the tubercle bacillus is so widely disseminated that few escape contact intimate enough to produce an appreciable tuberculous lesion. Nevertheless the protection afforded by this natural inoculation, although it modifies the course of disease resulting from a second infection, is obviously inadequate to prevent it, or to ensure a favorable outcome.

I shall enumerate some of the evidence that helps to explain the pathogenesis of the disease.

Tuberculosis in infancy and early childhood resembles that produced experimentally in susceptible animals, such as the guinea

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fig. A focus of infection is rapidly followed by tuberculosis of the lymph nodes situated in the direction of the lymph flow and the disease may progress with much greater rapidity in the lymph nodes than at the primary site of invasion. This relation does not exclude the possibility that the primary focus may occasionally be so small or regress so far that it becomes unrecognizable. Nevertheless Küss and later Ghon found a tuberculous focus in the lungs and lesion of the adjacent lymph nodes almost invariably associated. In only a small part of the children in this country, probably not exceeding 5 per cent, the primary site of invasion is the intestinal tract with secondary lesions in the mesenteric lymph nodes but in Great Britain approximately one-fourth of adults retain in the mesenteric lymph nodes scars of primary infection, acquired in childhood by way of the intestinal tract.

Pulmonary tuberculosis in adults has, however, little resemblance to tuberculosis produced by the usual inoculation of animals. It is a chronic disease that proceeds slowly, often with cavity formation but at the same time with a tendency to heal as indicated by the production of fibrous tissue. In sharp contrast with the tuberculosis of early childhood it long remains localized in the parenchyma of the lung and even though a whole lobe is implicated the lymph nodes at its hilum exhibit none of the characteristic changes of tuberculosis. This localization of the lesion at the site of invasion is reproduced in experimental animals only when an animal previously infected is reinfected with the tubercle bacillus. Koch found that a second infection, unlike the first, is followed by a prompt reaction, which tends to heal with no involvement of the nearest lymph nodes.

Renewed study of the anatomic pathology of tuberculosis has in very recent years extended our knowledge of the disease. Roentgenologic films prepared from lungs removed after death are an effective aid in the discovery of the calcified scars of healed tuberculosis acquired during childhood.¹ By this means, we seldom fail to obtain proof that those who die from the chronic pulmonary tuberculosis usual in adults have sustained an earlier infection. The characters of this form of the disease are not determined by changes in the lungs peculiar to increasing age but are the result of the increased resistance conferred by a first infection, as is shown by the now abundant evidence proving that pulmonary tuberculosis in a person who has escaped infection during childhood has all the characters of infantile tuberculosis. It extends rapidly in the lungs, implicates the adjacent lymph nodes and brings about massive caseous enlargement of them. Death often occurs, as it does in young children, from disseminated miliary tuberculosis. In such instances, occurring usually in colored adults, scars of existing infection cannot be found even when Roentgen ray films are used to aid the search.

Should the attempt be made to determine the significance of the

widespread prevalence of minor infections with tuberculosis demonstrated by anatomic lesions in the bodies of those who die from causes other than tuberculosis and by the corresponding frequency with which children react to tuberculin, two questions have outstanding importance: (1) What are the nature and limitations of the immunity conferred by infection? (2) What correlation exists between sensitization to tuberculin and immunity against the disease?

Observations made upon small laboratory animals beginning with the studies of Koch, Trudeau and Römer and a mass of evidence derived from experiments on cattle with the bovine vaccine of von Behring and other attenuated tubercle bacilli have shown that immunity against tuberculosis has several inconvenient features.

Resistance, though materially increased by a first infection, is readily overcome by increasing the reinfecting dose. This relation has been repeatedly demonstrated by varied experiments. Hamburger² even found that a small reinfecting dose injected into the skin on one side of a guinea pig produced a lesion that healed rapidly whereas a larger dose on the other side caused progressive tuberculosis.

Moreover such resistance as is conferred is transient and disappears after recovery from infection. Löwenstein has said, "Only the tuberculous animal is immune." Observations with the bovine vaccine of von Behring, for example, showed that resistance usually disappeared after a few months and rarely persisted after one year.

The degree of resistance conferred by inoculation increases with the virulence of the microorganism used. From the standpoint of human protection this relation is conspicuously undesirable for the agent that gives the greatest resistance to reinfection is itself a grave source of danger. This consideration is responsible for the total abandonment of the effort to protect cattle from spontaneous infection by inoculation with human tubercle bacilli (bovine vaccine of von Behring), for, as Theobald Smith and others showed, human tubercle bacilli may produce such advanced tuberculosis of the udder that tubercle bacilli appear in the milk.

Human pathology furnishes a significant illustration of the danger accompanying protective inoculation. The early tuberculous infections of childhood afford a certain degree of protection against reinfection and when it occurs profoundly modify its course, yet these childhood infections, as I shall show later, vary widely in intensity and even when long concealed or latent may ultimately cause active disease and death.

Efforts to protect by tubercle bacilli rendered harmless by destructive agents have had little success. Tubercle bacilli killed by heat produce some immunity against infection with the living microorganism but Trudeau found this resistance less than that which followed inoculation with an attenuated culture. Skin sensitization

after injection of the dead bacillus has been noted by some observers (for example, Baldwin) and denied by others. By repeated injection into the peritoneal cavity of guinea pigs Petroff and Stewart³ were almost uniformly successful in producing strong sensitization, which persisted for many months. These animals exhibited some increased resistance to infection (Zinsser, Ward and Jennings⁴) for they lived about six weeks longer than infected controls (Petroff and Stewart).

Inoculation of human beings with bovine tubercle bacilli attenuated by long-continued growth on media containing bile (BCG) has been introduced by Calmette and Guérin⁵ and is now widely practised. Their observations suggested that the immunity produced by it differs from that heretofore associated with experimental tuberculosis for they maintained that their bacillus was totally lacking in virulence and produced no tubercles when injected into animals. Observations by R. Kraus⁶ of Vienna and by Petroff, Branch and Steenkin⁷ have, however, shown that massive doses (5 mg.) will occasionally cause death of guinea pigs and it is now well recognized that the virus produces typical tuberculous lesions at the site of injection, in adjacent lymph nodes and occasionally elsewhere. Fed to infants by mouth as recommended by Calmette it seems to be harmless, but its efficacy when thus administered may still be questioned. There has been wide difference of opinion concerning the immunity that BCG produces in experimental animals.

Calmette has used the BCG virus to protect infants in contact with tuberculosis and has recommended its administration by mouth during the first ten days of life. The statistical evidence collected in this splendid endeavor indicates that the virus has some value but the validity of these statistics is in dispute. Protective inoculation would presumably have little value in children in whom a skin reaction to tuberculin showed that spontaneous infection had already occurred, for the virulent human bacillus would doubtless have already afforded a more effective protection. Furthermore protective inoculation at best evidently furnishes uncertain resistance against subsequent infection, for many children in whom tuberculosis of tracheobronchial lymph nodes is recognizable by roentgenologic examination of the chest, acquire apical tuberculosis if their contact with open tuberculosis is continued during adolescence.

There is no adequate understanding of the nature of the limited *immunity* of the tuberculous animal against reinfection. Agglutinin and complement fixing and bacteriotropic antibodies make their appearance in the blood serum but it has not been possible to determine exactly what part they play in the destruction of tubercle bacilli. Nevertheless it is highly probable that these bodies, notably bacteriotropic substances promoting the phagocytosis that is so

conspicuous during the progress of the disease, are essential factors in the struggle against the microorganism. Knowledge of the subject is astonishingly incomplete.

One phenomenon of immunity against tuberculosis and many other infections deserves, I believe, more consideration than it has received, namely, the heightened capacity of the reinfected animal to form antibodies. The first observations demonstrating that an animal once immunized forms antibodies more rapidly than a normal animal were made by Cole⁸ studying agglutinins for the typhoid bacillus. Mudd, Lucké, McCutcheon and Strumia⁹ in our laboratories have shown that animals when infected a second time form bacteriotropic antibodies, agglutinins and a substance promoting the wetting of tubercle bacilli much more rapidly after a second than after a first infection. It is desirable to learn whether the animal that has apparently lost its immunity after complete recovery from tuberculous infection still retains this power to immunize itself more rapidly than an animal previously uninfected.

One of the most puzzling phases of the pathogenesis of tuberculosis is the apparent paradox of hypersensitiveness and immunity. I shall avoid the term allergy because although it was introduced in order to include immunity it is used almost exclusively as a synonym for hypersensitiveness. Since hypersensitiveness is in great part at least the heightened capacity of the tissues to react with acute inflammation I shall discuss inflammatory reactions produced by the tubercle bacillus.

Much confusion has resulted from the attempt to define the relation of inflammation to tuberculosis. It is universally recognized by those who have directed their attention to the matter that tubercle bacilli when first introduced into the body produce all of the early phenomena of inflammation, with exudation of plasma, deposit of film and accumulation of polynuclear leukocytes. This phase of the reaction is transient and usually inconspicuous in comparison with the accumulation of mononuclear cells that follows. Information concerning the chemical constituent of the tubercle bacillus responsible for this reaction is no more accurate than that applicable to other microorganisms.

I shall not renew in detail discussion concerning the domain of inflammation in relation to tuberculosis. As with inflammation caused by other bacteria, accumulation of mononuclear cells is an essential part of the process. Use of the term "exudative" applied to accumulation of serum fibrin and polynuclear leukocytes and "proliferative" applied to the assembling of mononuclear cells has little to support it. Proliferation of the fixed tissue of the part becomes evident when collagen fibers are formed and is represented in its earliest stage by the reticular fibers of tuberculous tissue accurately described by Miller.

The accentuation of the early phases of inflammation character-

ized by redness, swelling and the accumulation of polynuclear leukocytes that occur with reinfection of a tuberculous animal was early recognized by the discovery of the tubercle bacillus and is an essential part of "Koch's phenomenon." It soon became evident to him that similar changes were produced by separable products of the tubercle bacillus. The tuberculin reaction is an acute inflammatory reaction, which when sufficiently intense proceeds to necrosis. Tuberculin (OT) or a water extract of tubercle bacilli introduced into the dermis of a normal guinea pig causes an inconspicuous inflammatory reaction with exudation of many polynuclear leukocytes still recognizable forty-eight hours after injection. The intense inflammatory reaction that occurs in a tuberculous animal is an accentuation of this process and does not differ essentially from it. Mononuclear cells assemble at the periphery of the lesion where the action of the irritant is least severe and gradually encroaching upon the polynuclear leukocytes ultimately replace them.

The changes at the site of reinfection with tubercle bacilli are the same in character. Jaffe and Löwenstein,¹⁰ Krause¹¹ and others have described the acute inflammatory reaction that occurs when the skin is the site of reinfection. Rapid accumulation of polynuclear leukocytes aid in the separation of necrotic tissue, superficial ulceration occurs and healing with new formation of fibrous tissue follows.

Changes that occur at the site of reinfection with tubercle bacilli resemble very closely those that occur in animals sensitized to foreign protein. Anaphylactic inflammation, or the Arthus phenomenon, occurs in animals, such as the rabbit, after repeated injections with a foreign protein like horse serum or egg white.¹² When the foreign protein is first injected into the skin of a normal animal it rapidly leaves the site of injection, produces no inflammatory reaction and enters the circulating blood, where it remains until antibodies, for example, precipitin, make their appearance. In the animal that has been immunized (and sensitized) reinjection with the foreign protein produces an intense inflammatory reaction with necrosis at the site of entry. I have shown that the foreign protein is arrested by the inflammatory reaction at the site of injection, from which it may be recovered almost quantitatively, and so fails to enter the circulating blood. The paradox between susceptibility to local inflammation and necrosis on the one hand and resistance, that is, immunity, on the other is only apparent, for the local inflammatory reaction is an effective means for the protection of internal organs.

Incidentally it is noteworthy that hypersusceptibility to foreign protein is referable to an antibody recognizable in the blood serum of the sensitized animal, for it can be passively transferred to a normal animal by injecting serum of one that is sensitized. Varied experiments have shown that whenever the antigen and this anti-

body are brought together in the tissues of a normal or immune animal, anaphylactic inflammation follows. The analogy between sensitization with foreign protein and the hypersusceptibility of the tuberculous animal to tuberculin is not complete for in the latter the intervention of an antibody, as shown by passive sensitization, has not been demonstrated satisfactorily. Nevertheless the analogy is supported from another point of view for the animal sensitized by tuberculous infection has the ability not possessed by a normal animal to fix tubercle bacilli at their site of entry.

Krause and Willis¹³ have recently demonstrated by inoculation of excised tissue into guinea pigs that there is in normal guinea pigs rapid dissemination of tubercle bacilli from the site of inoculation, whereas in animals previously infected dissemination is retarded. Transit of the bacillus from the point of entry in the skin to the axillary or inguinal lymph nodes, 4 or 5 cm. distant, was made in twenty-four hours or less but in animals rendered resistant by previous infection passage to the lymph nodes required two or three weeks. In the immunized animal some of the bacilli introduced into the skin ultimately reach distant parts of the body, but their number is relatively small.

Since acute inflammation is the immediate result of reinfection it is pertinent to inquire whether this reaction retards the dissemination of bacteria. A series of experiments recently performed with hemolytic streptococci has shown that inflammation of the peritoneal cavity caused by a sterile irritant, namely, aleuronat, in the early stages retards and after twenty-four or forty-eight hours completely prevents the rush of bacteria into the blood stream that invariably follows introduction of streptococci into the peritoneal cavity of a normal animal.

I have emphasized the foregoing relationship because with human tuberculosis inhibition of dissemination is one of the most conspicuous features of the disease in adults who have sustained the usual infection of childhood. In infancy and early childhood a focus of infection in the lung or intestine is immediately followed by tuberculosis of the regional lymph nodes and the lesion of the lymph nodes in most instances becomes much larger than the original focus. When the disease progresses, usually as the result of massive infection, death occurs from general dissemination of tubercle bacilli by way of the blood stream. Tuberculosis of the adult occurs with few exceptions in the lung and here first affects the apex. This lesion long remains localized in the apex and even when it spreads by way of the bronchial tree is limited to the lung. In contrast with the tuberculosis of infancy and early childhood pulmonary tuberculosis of adult type fails to implicate the nearest lymph nodes even when it is scattered over a whole lung. Some dissemination may occur in the terminal stages of fatal pulmonary tuberculosis of adults but miliary tuberculosis is rarely if ever seen.

Among school children of Philadelphia 54 per cent between the ages of five and nine years react to tuberculin; 76 per cent between ten and fourteen and 83 per cent from fifteen to nineteen years. In what degree can the reaction be used as evidence of immunity against tuberculosis? Both experimental and clinical evidences show that accompanying resistance is uncertain in the event of massive infection. Some writers have assumed that local susceptibility to tuberculin indicates hypersusceptibility to tuberculosis and Ranke,¹⁴ who assumed the occurrence of a primary, secondary and tertiary stage of tuberculosis analagous to the conventional stages of syphilis defined them as: (1) a stage of invasion; (2) a stage of hypersusceptibility with dissemination of lesions, and (3) a stage of chronic pulmonary tuberculosis with immunity. I have already assembled evidence that, I believe, is incompatible with this view; hypersusceptibility does not precede immunity but the two proceed hand in hand. Experimental evidence, as I have pointed out, indicates that the inflammatory reaction that tuberculin produces in a susceptible animal prevents dissemination of bacteria.

Nevertheless this reaction that is elicited by products of the tubercle bacillus even after they have undergone profound alteration, does not necessarily bring about destruction of the microörganism. It is well known that the reaction makes its appearance about the time when antibodies become demonstrable in the blood but is apparently well established before resistance has reached a maximum. Observations upon cattle made with the bovovaccine of von Behring furnish suggestive evidence that immunity is not necessarily accompanied by hypersusceptibility to tuberculin (Strelinger). The tuberculin reaction is conclusive evidence of tuberculous infection and the evidence at hand shows that it is inseparably associated with the phenomena of immunity. Its presence, like the otherwise dissimilar skin tests of diphtheria and scarlet fever, implies some immunity against infection but as yet it cannot be used as a measure of the degree of resistance.

Studies made by Lurie¹⁵ at the Henry Phipps Institute give very intimate information concerning the relation of the tubercle bacillus to the pathogenesis of the disease and help to explain why the lung suffers more severely than other organs, even when resistance is increased by preceding infection. He has followed the fate of tubercle bacilli in the lungs, liver, spleen, kidney and bone marrow of rabbits injected intravenously by both human and bovine tubercle bacilli and at varying intervals during the course of the infection has estimated the number of surviving bacteria by a method that enables him to count the number of colonies obtainable on suitable media from a weighed quantity of each organ. Tubercle bacilli, like other particulate matter injected into the blood stream, are deposited in greatest abundance in the spleen and in other organs in diminishing number in the order of liver, lung, bone marrow and

kidney. At first tubercle bacilli multiply in all of the organs, the human bacillus, in agreement with its behavior *in vitro*, more rapidly than the bovine. With the bovine type destruction of tubercle bacilli begins after four weeks in the liver, spleen and bone marrow and continues uninterruptedly, although the microorganism multiplies in the lung and to less extent in the kidney, until death ensues. With the human bacillus multiplication in the lung is far greater than in other organs and destruction here proceeds more slowly than elsewhere but in all of the tissues examined destruction begins between the second and fourth week and proceeds rapidly as the animal recovers. In rabbits reinfected with both human and bovine strains of tubercle bacilli there is no preliminary multiplication in any of the organs and destruction in liver, spleen and bone marrow follows inoculation immediately. Nevertheless even though the animals resist infection tubercle bacilli persist in the lungs in large number. It is noteworthy that a few tubercle bacilli survive for months in all of the organs of reinfected animals even though they exhibit no anatomic evidence of tuberculosis.

Knowledge of the widespread dissemination of tuberculous infection and the occurrence of reinfection suggest many new problems concerning the transmission of the disease. How are these latent infections acquired? Under what conditions does reinfection occur?

Experimental transmission by contact rather than by inoculation is a method of study that has not received the attention it deserves. The difficulties of investigating the spread of a disease that develops slowly during weeks or months are very great but can be overcome. The only systematic study of the experimental epidemiology of tuberculosis has been made by Perla¹⁶ at the Henry Phipps Institute. A large part of those who are engaged in the experimental study of tuberculosis believe that spontaneous tuberculosis of guinea pigs occurs seldom if at all, but as Koch recognized many years ago, it is a possible source of error in all experiments in which these animals are kept together in considerable number after they are infected with tuberculosis. When normal guinea pigs were kept in cages with others infected by way of the peritoneal cavity and with no superficial ulceration from 22 to 60 per cent acquired tuberculosis after seven months, the number varying with crowding and other conditions. Perla found that infected animals, in the latter period of the disease, eliminated tubercle bacilli with the feces and normal animals are infected by way of the gastrointestinal tract with secondary involvement of the mesenteric lymph nodes. Dr. Lurie has continued these experiments and has found that vaccinated animals resist infection. The method of study, though laborious, promises to aid the solution of important questions concerning the transmission of tuberculosis.

At the present time the epidemiology of human tuberculosis can be studied more satisfactorily than that of animals. In the past this

study has been pursued in large part by statistical methods with disappointing result for there is today nearly as much uncertainty concerning the contagion of phthisis as there was centuries ago.

Until the last few years nothing has been known concerning the distribution and severity of tuberculous infection among those who give no evidence of the disease and are presumably in good health. We have been wholly ignorant of the relation of latent infections to clinically manifest disease and of the conditions under which latent infection becomes manifest disease.

It is evident that no accurate knowledge of the epidemiology of tuberculosis is obtainable as long as these latent infections are ignored. As little could be learned concerning the epidemiology of influenza if it were arbitrarily agreed that attention should be limited to those who developed pneumonia.

Study of the pathologic anatomy of latent tuberculous infection has directed my attention to the need of accurate knowledge concerning its occurrence during life and its mode of spread. Two means are available for the discovery of lesions unaccompanied by significant symptoms or physical signs, namely, the tuberculin reaction and roentgenologic examination. Roentgenologic examination of the chest, successfully performed only when many obstacles are overcome, is an effective and often exact method of depicting the extent of anatomic changes caused by tuberculous infection. Unfortunately it does not reveal some of the earliest changes.

During the last five years the dispensary of the Henry Phipps Institute has been organized to assemble by its routine operation information concerning the occurrence of latent as well as clinically manifest tuberculosis, to trace the spread of infection by contagion within the household and elsewhere and finally to determine by observations continued over a period of years under what conditions latent develops into manifest disease. This endeavor has been in large part successful and has evolved a dispensary system that, from a wholly practical standpoint, is an effective means for the prevention of tuberculosis.

The essential features of the procedure are as follows:

Search for latent as well as manifest tuberculosis and the attempt to determine whether it is sufficiently advanced to menace health.

Routine application of the intradermic tuberculin test interpreted in relation to the age and to the character of the associated lesions.

Roentgenologic chest examinations directed to determine the position and extent of latent and clinically manifest lesions and repeated often enough to reveal the progress of the disease.

Social service by a nursing staff trained to give care to patients and their families and to collect information not obtainable from the patient.

The preparation of a graph that pictures the origin and progress of tuberculosis both manifest and latent within the household.

Investigation of the family as a unit of infection, and prophylactic care guided by all the information that has been assembled.

A study of the spread of tuberculosis in families has been undertaken by Dr. McPhedran and the author.¹⁷ The usual method of sputum examination, if repeated often enough, is an accurate measure of the danger to which a household is exposed. In families in which some member suffered with tuberculosis and expelled tubercle bacilli with the sputum, the incidence of latent tuberculosis, as indicated by the tuberculin test, was very high; 80 per cent of children of contact families react to tuberculin before they reach their fifth year of life, whereas at the same age less than 30 per cent of children are sensitive to tuberculin.

Furthermore roentgenologic examination revealed latent or manifest tuberculous lesions four times as frequently in contact as in noncontact families and showed that the lesions in contact families were far more severe in character and extent. Latent tuberculosis of the tracheobronchial lymph nodes occurred seven times as often in contact as in noncontact families. Approximately 1 in 10 of the children exposed to open tuberculosis had acquired manifest tuberculosis before they had reached adult life.

This study conducted during a period of five years has demonstrated for the first time how frequently advanced latent lesions develop into manifest disease. The recognition of advanced latent tuberculosis furnishes a means by which the onset of tuberculosis may be predicted within certain limits years even before it has begun to undermine health. These observations have demonstrated the value of repeated roentgenologic examination of children exposed to tuberculosis and make it possible to forestall by appropriate prophylactic care the transition of advanced latent into manifest disease.

During early childhood two lesions, recognized by roentgenologic examination in combination with the tuberculin test, are especially significant as precursors of manifest disease, namely, diffuse infiltration of the lung parenchyma identified as tuberculous and tuberculosis of tracheobronchial lymph nodes.

Infiltration of lung parenchyma occurring in young children and seldom situated in the apex is recognized by roentgenologic examination and is usually associated with a very active tuberculin reaction though unaccompanied by symptoms or physical signs of pulmonary disease. Tuberculosis of tracheobronchial lymph nodes is doubtless, as autopsies show, invariably associated with the lesion but moderately enlarged caseous lymph nodes are not recognizable unless they have undergone some calcification. Nevertheless tuberculosis of tracheobronchial lymph nodes, evident in Roentgen ray films, is associated with infiltration of the parenchyma in about half of all instances. The lesion of the lung parenchyma that remained latent during months or even years of observation may finally manifest

itself by cough, loss of weight, fever and physical signs over the affected area.

Tuberculosis of tracheobronchial lymph nodes evident by roentgenologic examination in more than one-fifth of children exposed to open tuberculosis seldom produces recognizable symptoms or physical signs but is in many instances the precursor of manifest disease of the lung. This in younger children has the character of the pulmonary infiltration just described and is due to progressive increase of the primary focus of infection, which was not visible when the tracheobronchial lesion was first recognized.

In adolescent children, however, the pulmonary lesion like that of adult life makes its appearance in the apex of the lung, bears no anatomic relation to the lesion of the bronchial lymph nodes as autopsies show and appears after this lesion has undergone calcification. When the two lesions occur in a child long in contact with open tuberculosis it is probable that apical tuberculosis is due to continued exposure to the source of infection responsible for the tracheobronchial lesion. The latter is evidence of exposure to open tuberculosis and protection from further infection may prevent manifest disease.

Mortality from tuberculosis reaches a high peak during the first year of life, falls rapidly during the second year and gradually diminishes during several subsequent years. From the fifth to the fifteenth year the death rate from the disease is lower than at any other time of life. From the twelfth year to the fifteenth year in girls and somewhat later in boys, the death rate from tuberculosis begins to rise and reaches a maximum in early adult life. Tuberculous infection in the period between the fifth and fifteenth years has the characters of the disease of childhood and it tends to pursue a benign course. In adolescence the adult apical type makes its appearance and the death rate from tuberculosis begins to increase.

Roentgenologic studies at the Henry Phipps Institute have revealed the frequency with which apical lesions occur in adolescent children of families exposed to open tuberculosis. These children are often in excellent health and just as often over- as underweight. Apical lesions may pursue a benign course but not infrequently after a few months, or more frequently after several years, the characteristic symptoms and physical signs of pulmonary tuberculosis ensue. We have repeatedly followed its course from the appearance of a small shadow below the margin of the second rib with no other evidence of disease, during a period of gradual extension of the lesion, until active disease is manifested by symptoms, physical signs and tubercle bacilli in the sputum. Years ago Newsholme pointed out the long latent period between exposure to infection and the onset of phthisis. The latent apical lesions of adolescence are precursors of a large part of the phthisis of early adult life. Recognition of these latent lesions and the application of well-established

procedures to prevent further extension of tuberculous infection promise to become important factors in the control of the disease.

The opinion upheld by von Behring and many others that all tuberculosis is acquired in early childhood still has many supporters. The strongest evidence in favor of the view that adults do not acquire the disease is derived from statistics that show the incidence of the disease among husbands or wives of consumptives. Vast figures representing the histories of over 50,000 persons who have been exposed to marital infection have failed to give decisive information concerning adult infection.¹⁸ The accuracy of the mathematical methods of Pope and Pearson and others who have investigated the problem can scarcely be doubted but the value of the data they have used is at least questionable. Direct observations continued during a period of years with the aid of roentgenologic examination, which on the one hand is an effective aid to the diagnosis of manifest tuberculosis and on the other hand discloses tuberculous infection unaccompanied by symptoms or physical signs, give more trustworthy information. In a small group of families in which husband or wife suffered with open tuberculosis we found evidence that the infection had been transferred to the consort in nearly half of those whom it was possible to examine. Subsequent observations continued during the last five years have amply confirmed this observation. Both manifest and latent tuberculosis is far more common in the consorts of persons suffering with open tuberculosis than in those not exposed to marital infection.

Infection from without during adult life can scarcely be doubted. Nevertheless endogenous infection from a preëxisting lesion cannot be denied; indeed it is probable that in a person who has become resistant as the result of existing infection endogenous and exogenous infection would have similar results. All of the evidence that is available indicates that the pulmonary tuberculosis of adults is acquired with few exceptions from without. This is certainly true of the marital infection just described. Anatomic evidence proves that the apical tuberculosis of adults is not the result of extension from the focal lesions of first infection for the two are usually separated widely and as often in opposite as in the same lungs. Study of the bacteriology of focal nodules of first infection in the lungs and bronchial lymph nodes, made by Dr. Aronson and the author,¹⁹ show that tubercle bacilli have disappeared when encapsulation begins so that the lesions of first infection are free from tubercle bacilli at a time when the apical lesion of adult type makes its appearance.

Webb²⁰ objects to this conception of the pathogenesis of tuberculosis because he says we know no other parasite that must twice infect the same host in order to complete its life history. Two infections of the host are, however, not essential, for the lesion of first infection by caseation into a bronchus might transmit the disease and this was doubtless the primitive mode of transmission.

Theobald Smith has suggested that the tubercle bacillus tends to adapt its virulence to the resistance of its host so that it may produce a long-continued disease favorable to its dissemination. With widespread latent infection virulence might be modified to produce long-continued disease in a partially immunized host.

A survey of tuberculosis among children in the public schools of Philadelphia made by Dr. Hetherington, Dr. McPhedran, Dr. Landis and the author during the last three years has extended our knowledge of the epidemiology of the disease and revealed the frequency with which infection varying in character and extent occurs in children who are presumably healthy. One purpose of the survey has been to determine what children have such grave infections that they require care in the open-air schools now maintained by almost all of the large cities of this country. It is noteworthy that the system of medical inspection of schools in Philadelphia is highly efficient and excludes from the school tuberculosis recognizable by the usual procedures. All of those who have given attention to the matter admit that the usual methods of physical diagnosis discover tuberculosis only after it is far advanced and can be benefited if at all only by sanatorium treatment or its equivalent. Loss of weight, as Hetherington²¹ has shown, is a late manifestation of tuberculosis and cannot be used as a criterion of grave latent infection. By tuberculin tests, roentgenologic films and physical examination, we have sought to find the various types of latent infection discussed in this lecture.

The results of tuberculin tests made by the intradermic method upon 4100 children suggest some conclusions of general interest. Classified in accordance with age they show that the incidence of the reaction increases from 47.2 per cent at the age of five years to 95.3 per cent at eighteen. They furnish no support to the opinion that the prevalence of concealed infection has diminished parallel with the diminishing mortality from tuberculosis in recent years. Our figures do not differ materially from those collected by Hamburger and Monti twenty years ago in one of the most crowded cities of Europe, namely, Vienna. Furthermore, not only is latent tuberculosis so widespread that few children escape before they reach adult life but in many instances it is so advanced that it is a grave menace to life. The astonishing prevalence of these advanced infections suggests that mortality from tuberculosis will promptly increase if conditions favorable to the disease should reappear.

Our survey has shown that 0.5 per cent of the school children we examined have manifest tuberculosis recognizable by physical examination and roentgenologic films. Latent tuberculous infiltration of the lungs of the type of childhood was found in 2 per cent of children and was evidently more significant in younger children. Latent apical tuberculosis (adult type) was found in 1 per cent of

children, in large part in high-school pupils between the ages of fifteen and eighteen years.

Both sex and race modify the frequency and severity of tuberculous infection in school children.

Minor infections indicated by tuberculin tests and calcified nodules in lungs and lymph nodes are somewhat more frequent in girls than in boys but the graver latent infections, revealed by infiltration of the lung parenchyma and especially by latent apical infection, are much more frequently found in girls than in boys. Particularly significant is the high incidence of clinically manifest tuberculosis in adolescent girls. Of boys of high-school age only 0.4 per cent had clinically recognizable tuberculosis whereas of girls 1 per cent were affected.

We have found minor tuberculous infection less frequent in colored than in white children but graver infections and especially clinically manifest disease are found much oftener in colored than in white children. Manifest tuberculosis was found in 0.6 per cent of white children between twelve and eighteen years of age and in 2.4 per cent of colored children of the same ages. Protective infection seems to occur less frequently in the colored than in the white and when colored children are infected with tuberculosis, especially during adolescence and early adult life, grave disease is more likely to ensue.

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REVIEWS.

RICKETS, INCLUDING OSTEOMALACIA AND TETANY. By ALFRED F. HESS, M.D., Clinical Professor of Pediatrics, University and Bellevue Hospital Medical College, New York City. Pp. 485; 52 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.50.

SINCE the publication of Dick's book in 1922, an immense amount has been written on the subject of rickets. The realization of its widespread prevalence and the invasion of its field advertising copy have aroused an enthusiasm in research unsurpassed by any field of modern medicine.

Beyond doubt the one most fitted for such a duty, Hess has collected the researches of workers the world over, has scanned their results and evaluated their conclusions in this book, which, be it clearly understood, is a monograph and not a handbook.

Separate chapters are devoted to etiology, pathogenesis, pathology symptomatology, diagnosis and treatment. Each is discussed fully and a bibliography appended. The matter of the metabolism is considered separately and there is a splendidly illustrated chapter on the radiographic changes of rickets.

The chapter on treatment is gratifying complete and of special interest because of the recent questioning of the harmlessness of irradiated ergosterol. The author's endorsement of it, his recommendations as to dosage and his precautions as to its use, should be known to every pediatricist.

The Reviewer feels that this was a much needed book and that in it the need has been most admirably filled. It should be in the possession of every pediatricist and student of metabolic diseases.

J. S.

SURGICAL DISEASES OF THE THYROID GLAND. By E. M. EBERTS, M.D., Surgeon to the Montreal General Hospital, Associate Professor of Surgery, McGill University, with the assistance of R. R. FITZGERALD, M.D., and PHILIP G. SILVER, M.D. Pp. 238; 48 engravings. Philadelphia: Lea & Febiger, 1929. Cloth, Price, \$3.50.

IN the preparation of this volume, the authors have drawn largely upon their personal experience at the Goiter Clinic of the Montreal General Hospital. They have clearly and concisely presented

practically all that is known and much that is theory concerning the thyroid gland and its diseases.

The first part of the book is given over to a consideration of the embryology, anatomy, physiology and pathology. The second part discusses the clinical side of the various forms of goiter. Except for a few suggestions, very little space is given to the operative technique, but the chapters on preoperative and postoperative treatment are excellent. Throughout the clinical part of the book, case reports are used to illustrate the text, perhaps in too great profusion. At the end of many chapters is given a short bibliography.

The monograph is well written, and is highly recommended to those who are interested in the diagnosis and treatment of thyroid diseases.

L. F.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. By VARIOUS AUTHORS. Vol. III. ECONOMIC BACTERIOLOGY, PLAGUE, ANAEROBES, FOOD POISONING. Pp. 413; 13 illustrations. London: His Majesty's Stationery Office, for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9, for this volume; for the set, £8.14.9.

AN authoritative and adequate System of Bacteriology in English is indeed a boon to contemporary medical science. Those who have sufficient German are so used to turning to German sources and those without German to doing without this aid to investigation that it will be an especially pleasant change to have this source of information in our own language. The British National Research Council has therefore again put the medical profession in its debt by fostering this monumental undertaking. With the unavoidable constant increase in medical specialization, such works become increasingly necessary in facilitating acquisition of information in a perhaps closely related but little known field. As Lord Balfour, Chairman of the Medical Research Council, says in the General Preface, "No investigator, however narrow may be his intensive study of one aspect of one problem, need henceforth feel that in cultivating this small part he must lose his vision of the whole; and no one endeavoring to the best of his ability to form some general picture of the whole need doubt that with the aid of this System of Bacteriology he will succeed in his efforts."

This third volume—the first published—deals with such topics as the Economic Aspects of Bacteriology (Thaysen); the Bacteriology of Water (Henry); of the Dairy Industry (Vollum); of Foods (Savage); of the Soil (Thornton); Bacterial Diseases of Insects (St. John-Brooks); of Plants (Paine); Gas Gangrene (Robertson and O'Brien); Bacillus Pestis (Petrie and Bulloch); Bacillus Tetani (Fildes and

others); *Bacillus Botulinus* (Hewlett and others) and Bacterial Food Poisoning (Savage).

It is beyond the scope of this review or the ability of the Reviewer to evaluate these chapters in detail, but many of the names should carry sufficient conviction in themselves. A further recommendation in these days of reckless bookmaking and charging is the very modest price—a guinea for a volume of this kind, or less than 9 pounds for the set of 9 volumes, is a refreshing relief from the prices charged in Germany especially and to a lesser extent in this country. Let us hope in the interests of science that it will have a correspondingly wide sale.

E. K.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. IV. THE ENTERIC GROUP, VIBRIOS, PASTEURELLA. By VARIOUS AUTHORS. Pp. 482. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

THE chapter of 85 pages on "*Bacillus Typhosus*" is apparently written mostly by D. Harvey, though designation of the parts written by the associated authors is not clearly made. The introductory historical section seems inadequate; Bretonneau's contribution is overemphasized, Gerhard's entirely omitted. On page 35 it is stated that the hematohepatogenous route of infection is probably the usual one in man, yet on page 39 the more conventional route of passage through the intestinal wall of the lymph spaces, nodes and spleen is supported. More than half of the 167 references are to British sources, an imbalance probably due to greater familiarity with the native literature than to conscious chauvinism. Perhaps for the same reason, the American literature seems to the Reviewer specially to have been neglected in spots. Much space is properly devoted to serologic reactions and immunization. Dreyer's quantitative agglutination estimation—the important British contribution to this phase—is mentioned but will be described in Vol. IX. The invaluable immunization experiences of the war are emphasized, though Leishman's earlier work and that of Russell in the American Army mostly or entirely omitted from consideration. It is not meant to imply, however, that such shortcomings detract materially from the value of the presentation as a whole.

While space forbids a similar discussion of the other chapters on the *Salmonella* Group, Dysentery, Colon Groups, Cholera Vibrio, *Pasteurella Trevisan* and *Bacillus Pseudotuberculosis Rodentium*, it can safely be asserted that they are valuable contributions to the subject. The lack of uniformity in presenting references—some at end of chapters, others at end of sections—is a minor regrettable item.

E. K.

INTERN'S HANDBOOK. By Members of the Faculty of the College of Medicine, Syracuse University, under the direction of M. S. DOOLEY, A.B., M.D., Chairman, Publication Committee. Pp. 236. Philadelphia: J. B. Lippincott Company, 1929. Price, \$3.00.

THIS little book should be of inestimable value to every intern. It presents in small space a wonderful amount of important knowledge that otherwise must be obtained from one of a dozen textbooks. Much useful information is given on drugs, their action, costs, advantages, and so forth, together with a pharmacy list. Standard clinical procedures, medical, surgical and special dietaries, techniques and routine lists, all are clearly and succinctly presented. Instructions as to the conduct of action in emergencies is given clearly and in detail.

The book is a "find" for any intern.

B. E.

DISEASES AND DEFORMITIES OF THE SPINE AND THORAX. By ARTHUR STEINDLER. Pp. 573; 76 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$12.50.

DOCTOR STEINDLER has added another valuable monograph to the literature of orthopedics.

The case matter presented is excellent and is apparently entirely from the author's clinic. The opinions expressed are entirely personal and although they may not meet with general agreement they are so firmly founded upon fact and experience as to demand most careful consideration.

The illustrations are many and excellent. The assembly of the material in outline form adds greatly to the ease of reference and assures logical sequence of substance. While the inclusion of basic facts and experimental data makes of this book an authoritative treatise which is highly recommended to both general practitioner and orthopedic surgeon.

G. W.

SURGICAL AND MEDICAL GYNECOLOGIC TECHNIC. By THOMAS H. CHERRY, M.D., Professor of Gynecology, New York Post-Graduate Medical School and Hospital. Pp. 678; 558 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$8.00.

ANY author who has sufficient energy to illustrate his own work after writing the text deserves critical praise. Cherry has profusely illustrated the operations discussed, some of the drawings being

really creditable while others are very inferior, many being repeated several times. The book is essentially a treatise on the author's methods and experience and contains no bibliography. The inclusion of hernia, intestinal operations and obstetrical procedures and the arrangement of the illustrations make the book unduly large. In the section on medical treatment the author enthuses over the value of diathermy. More careful editing could eliminate such spelling as "*fascia endoplevina*," MacKenrodt, procidenture and vulva outlet. With no desire to be unfair or hypercritical, the Reviewer regards the work as just another book. F. B.

THE HISTORY OF HEMOSTASIS. By SAMUEL CLARK HARVEY, M.D., Professor of Surgery, Yale University, Surgeon in Chief, New Haven Hospital. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$1.50.

BLEEDING, even as early as broken bones, must have aroused the therapeutic skill of our prehistoric ancestors. Hemostasis, then, should have a history coeval with surgery and even today its known beginnings can be traced to the earliest civilizations. The present book—one of Hoeber's attractive historico-biographical series—deals chiefly with the cautery, the ligature and the tourniquet, though Lister and his scientific study of various ligatures, the effect of infections and so on, receive adequate and sympathetic consideration. Just as in the larger subject it is interesting to see how knowledge that had been painfully won through centuries was lost perhaps for centuries again, only to be relearned with more travail.

E. K.

GONORRHEA AND KINDRED AFFECTIONS IN THE MALE AND IN THE FEMALE. By GEORGE R. LIVERMORE, M.D., F.A.C.S., Professor of Urology, Medical Department, University of Tennessee; and EDWARD A. SCHUMANN, A.B., M.D., F.A.C.S., Associate Professor of Obstetrics, University of Pennsylvania. Pp. 245; 66 illustrations. New York: D. Appleton & Co., 1929. Price, \$5.00.

THIS book represents the earnest efforts of two exceptionally capable men to break into a hard field; one where so little is new and so much is personal opinion and experience. They have been successful in presenting the subject devoid of radicalism and divested of the advocacy of any current therapeutic fad. Its conservatism is its best factor.

The first 127 pages cover acute, chronic and metastatic gonorrhea in the male. The preface promises "great attention" to pathology that is scantily borne out and wretchedly presented in 28 lines.

The authors preach gentleness in treatment but advocate drugs, in practice that some might call heroic, until one wonders if the pessimism voiced under prognosis is not the just results of the treatment used.

The remaining 131 pages devoted to the problem in the female are easy, concise reading and admirably presented. Its optimism is in contrast to the pessimism of the fore part, and one catches a glimpse of the gynecological viewpoint which recognizes the disease self-limited, while in the male (with its simpler problem) too many are still striving for the sterilisans magna, and believe that they, with their drugs, cure gonorrhea.

A. R.

BOOKS RECEIVED.

. NEW BOOKS.

De Oculis.* By BENEVENUTUS GRASSUS. Translated by CASEY A. WOOD, M.D., LL.D. Pp. 101; 5 illustrations. California: Stanford University Press, 1929. Price, \$5.00.

Common Infections of the Female Urethra and Cervix.* By FRANK KIDD, M.A., M.Ch. (CANTAB.), F.R.C.S. (ENG.) and A. MALCOLM A. SIMPSON, B.A., M.B., D.P.H. (CANTAB.). Pp. 197; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

Human Helminthology.* By ERNEST CARROLL FAUST, Ph.D. Pp. 616; 297 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$8.00.

Laboratory Methods of the United States Army.* EDITED BY CHARLES F. CRAIG, M.A., M.D. Pp. 696; 9 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$3.50.

A System of Bacteriology in Relation to Medicine.† By Various Authors. Vol. III. Pp. 413; 13 illustrations. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

A System of Bacteriology in Relation to Medicine.† By Various Authors. Vol. IV. Pp. 482. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

Oxford Monographs on Diagnosis and Treatment. EDITED BY HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Vol. V. *The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract*.* By ELMER H. FUNK, M.D. Pp. 618; 182 illustrations. New York: Oxford University Press, American Branch, 1929.

Oxford Monographs on Diagnosis and Treatment. EDITED BY HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Vol. VI. *The Diagnosis and Treatment of Arthritis*.* By RUSSELL L. CECIL, M.D., Sc.D. Pp. 216; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

* Reviews of titles followed by an asterisk will appear in a later number.

† See this issue.

- Surgical Clinics of North America (Philadelphia Number).* Vol. IX, No. 5. Pp. 299; 111 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, paper \$12.00; cloth, \$16.00 per clinic year.
- Gastric and Duodenal Ulcer.** By ARTHUR F. HURST, M.A., M.D. (OXON), F.R.C.P., and MATTHEW J. STEWART, M.B. (GLASG.), F.R.C.P. Pp. 544; 159 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$20.00.
- Hemorrhoids.** By CHARLES CONRAD MILLER, M.D. Pp. 124; 20 illustrations. Chicago: Modern Surgery Publications, 1929.
- Stone and Calculous Disease of the Urinary Organs.** By J. SWIFT JOLY, M.D. (DUB.), F.R.C.S. (ENG.). Pp. 568; 189 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$16.00.
- The Nervous System.** By E. E. HEWER, D.Sc. (LOND.) and G. M. SANDES, M.B., B.S. (LOND.), M.R.C.S., L.R.C.P. Pp. 104; 55 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$6.50.
- The Science of Nutrition Simplified.** By D. D. ROSEWARNE, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 314; 7 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$3.50.

NEW EDITIONS.

- Modern Methods of Treatment.** By LOGAN CLENDENING, M.D. With Chapters on Special Subjects by Various Collaborators. Third edition. Pp. 815; 95 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$10.00.
- The Blood Picture.** By PROF. DR. VICTOR SCHILLING. Translated and Edited by R. B. H. GRADWOHL, M.D. Seventh and eighth revised edition. Pp. 408; 48 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$10.00.
- Memoranda of Toxicology.* By MAX TRUMPER, B.S., A.M., PH.D. Second edition. Pp. 214. Philadelphia: P. Blakiston's Son & Co., Inc.
A convenient booklet for emergencies, with compact information easily available. Recent developments, such as barium, tetra-ethyl lead, methyl chloride, etc. are properly considered.
- Synopsis of Midwifery and Gynecology.* By ALECK W. BOURNE, B.A., M.B., B.Ch. (CAMB.), F.R.C.S. (ENG.). Fourth edition. Pp. 434; 171 illustrations. New York: William Wood & Co., 1929. Price, \$4.50.
- Practical Local Anesthesia.** By ROBERT EMMETT FARR, M.D., F.A.C.S. Second edition. Pp. 611; 268 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$9.00.
- Disorders of the Sexual Function.* By MAX HUHNER, M.D. Third edition. Pp. 342. Philadelphia: F. A. Davis Company, 1929. Price, \$3.00. Enlarged with a new chapter on Dysmenorrhea.
- Practical Massage and Corrective Exercises.** By HARTVIG NISSEN. Fifth edition, revised and enlarged. Pp. 271; 72 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$2.50.
- The Nervous Child.** By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.). Fourth edition. Pp. 249; 8 illustrations. New York: Oxford University Press, American Branch, 1929.
- Pettibone's Physiological Chemistry.** By J. F. MCCLENDON, PH.D. Fourth edition. Pp. 368; 17 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$3.75.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Clinical Classification of Congenital Cardiac Disease. — ABBOTT (*Lancet*, 1929, ii, 164) writes that clinicians do not always recognize the fact that congenital cardiac disease does not necessarily mean "blue baby" with its usual symptom complex. This particular type of congenital disease is of interest, but cannot be affected by the physician's skill since there are unalterable structural changes in the heart. There exists, on the other hand, a larger and much more important group of congenital cardiac patients to whom the word "acyanotic" applies. This group is of considerable importance to the physician because these patients have a relatively good expectation of life and may live to an advanced age without disturbances from their defect. It is for this reason that it is advisable to recognize this particular type. This "acyanotic" group is divided by her into two divisions. In the first there is mechanical interference with the circulation such as may be produced by pericardial defects, congenital heart block, pulmonary and tricuspid insufficiency, aortic and mitral stenosis, anomalies of the coronary arteries, and a few more rare conditions. In the second group the patients have arterial-venous shunt and possibly terminal or transient cyanosis with such defects as patent foramen ovale, multiple defects of the interauricular septum, localized defects at the base of the interventricular septum, patent ductus arteriosus, and localized defects of the aortic septum.

Antirabic Vaccination by Means of Desiccated Virus. — The director of the laboratories of Charity Hospital of Louisiana, D'AUNOY, reports (*Am. J. Pub. Health*, 1929, 19, 986) upon the patients bitten by rabid animals treated during the past fourteen years with desiccated virus as prepared by the technique proposed by Harris and modified to a certain

extent. As a unit is designated the minimal infective dose; that is, the least amount of the desiccated material which within five days after preparation, kept at a temperature of -12°C. , will cause paresis in a 2400 gm. rabbit within seven days following intracerebral injection. This minimal infective dose is between 0.002 and 0.004 mg. The initial dose is 250 units, doubling the quantity daily until a maximum of 2000 is reached. A total of 12 treatments is given the average patient, except in severe injuries of the face and scalp when 15 treatments, equivalent to 25,750 units, are given. There have been 5125 patients treated with the virus. About 25 per cent. of the patients had a slight constitutional reaction and about 10 per cent, an allergic reaction. Three cases of treatment paresis occurred, one of which terminated fatally from an ascending infection of the urinary tract after paralysis of the lower extremities. There have been five deaths occurring in the series due to nonprotection. Of a total number of cases in which prophylactic antirabic vaccinations were given, 2380 of these were given to protect against injuries by proven rabid animals. The figures that have been compiled by D'Aunoy speak for themselves. They represent a really very remarkable series of patients protected against rabies.

SURGERY

UNDER THE CHARGE OF

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PHILADELPHIA, PA.

Treatment of Torticollis.—HOWELL (*British Med. J.* 1929, 2, 714) says this paper has been written and these photographs of the cases before, during and after treatment have been shown in order to emphasize that torticollis may be prevented by careful antenatal examination of the mother to secure the simplest presentation avoiding natal injury. Further the younger the infant is, the sooner the cure. Lastly, the subcutaneous tenotomy of the sternomastoid muscle gives a complete, lasting scarless result.

Nodular Goiters—Their Relation to Neoplasia.—GRAHAM (*Am. J. Surg.*, 1929, 7, 163) believes that the development of the nodular goiter is in all probability dependent upon a single process or mechanism rather than upon multiple processes or mechanisms of fundamentally different character. Differences in degree of reversion growth, encapsulation and structural departure from otherwise normal thyroid tissue offer a satisfactory explanation of the gross and microscopic variations observed in nodular goiters. Such a conception obviates the necessity of invoking an embryologic defect for which insufficient objective evidence has been adduced to explain the so-called fetal adenoma of Wölfler. Nodular thyroids associated with endemic goiter, hypothyroidism and hyperthyroidism are intimately related in point of origin

to the hyperplastic phase of thyroid over growth rather than to the involutional phase. The latter may be a factor of some importance in determining the morphologic character of the end result. The process of nodulation may have its inception in fetal life, postnatal life, during puberty, adolescence or adult life. From a morphologic standpoint the end results of the process of nodulation, that is the encapsulated mass of nonlobulated thyroid tissue should be included in the category of benign glandular neoplasms.

Cases of Unsuspected Carcinoma of the Prostate.—BUGBEE (*J. Urol.* 1929, 22, 363) noted that small carcinomata are found in the lateral and median lobes of the prostate which may be diagnosed only on microscopic section after removal. A more careful study of all prostates may make it possible to detect small suspicious areas leading to a prostatectomy in some cases where otherwise palliative measures might be continued. The sudden onset of retention in the presence of comparatively mild urinary symptoms may be suggestive of malignancy. Prostatectomy may be carried out quite as easily in these cases as in simple hypertrophy. Preliminary suprapubic drainage, allowing edema and infection to subside is an advantage. There is no evidence to point to the fact that the small amount of trauma incident to the removal of these prostates has caused a squeezing out of cancer cells into the lymphatics and a consequent spread of the disease.

Diagnosis of Perforated Peptic Ulcer.—VAUGHAN and SINGER (*Surg., Gynec. and Obst.*, 1929, 49, 593) state that seventy-two patients diagnosed as having perforated ulcer were examined radiologically for pneumoperitoneum at the time of admission to the hospital. In 63 of the 72 patients the diagnosis of perforated ulcer was definitely established; 87.5 per cent of these had free intraperitoneal air as determined fluoroscopically. In the 9 remaining patients the evidence of perforated ulcer was not conclusive inasmuch as pneumoperitoneum was absent. Laparotomy was not performed and autopsy was precluded by recovery. The clinical picture in the nine unproven cases corresponds to that seen in perforations which become spontaneously sealed following the escape of a limited amount of gastric or duodenal content. The reason for the lesser frequency of pneumoperitoneum in these *formes frustes* cases is probably the same which explains the mildness of the course, viz.; a small leak with a trifling leakage.

Syphilis of the Stomach.—SINGER (*Am. J. Syph.*, 1929, 13, 391) claim that a large number of cases presenting anatomically the features of linitis plastica have been reported as instances of gastric lues. Direct evidence pointing to a causal relationship between lues of the stomach and linitis plastica is obtained from the data in a case of syphilitic pangastritis reported by Windholz in which a patient was laparotomized, a biopsy obtained from the stomach, antiluetic treatment administered and the stomach secured some time later at autopsy. A comparison of the gross and microscopic features of the stomach at the time of operation with those found at autopsy indicated a transformation of a localized luetic gastritis into a circumscribed linitis plastica. In addition to direct testimony in direct evidence of a close association between

syphilitic inflammation and contraction of the stomach can be adduced from a clinical and anatomic and a combined clinicopathologic study. A joint clinicopathologic investigation has demonstrated that the more one seeks clinical indications of lues in the presence of an anatomic linitis plastica the more frequently does one find a positive Wassermann test and other indications of syphilis.

Chronic Cystic Mastitis.—BLOODGOOD (*Ann. Surg.*, 1929, 90, 886) says that this is not a precancerous lesion any more than the lactating breast, but it may present microscopic pictures difficult to differentiate from cancer. More and more breasts are being sacrificed, the author believes, needlessly. In order to give all women who may have a cancerous lump in the breast at least 70 per cent chances of a cure we must bring them all under observation within a month. In probably 70 per cent of these cases any operation can be decided against by palpation alone. Of the 30 per cent in which the breast must be explored in one-half or more the benignancy of the lesion can be recognized by a combination of gross inspection and immediate frozen section.

THERAPEUTICS

UNDER THE CHARGE OF

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The Therapeutic Effect of Insulin Administered by Mouth.—Following his experiences with the oral administration of adrenal cortex, STEPHAN (*München. med. Wchnschr.*, 1929, 38, 1579) observed that when the dried substance of insulin or its salts were suspended in digestible fats and oils and administered in postabsorptive state, the blood-sugar level was lowered. Further observation showed that it was essential that bile should be present in the stomach if the insulin-oil suspension was to exert its effect. It was suspected, therefore, that an insulin-bile-acid combination is essential for the absorption of insulin after oral administration. Experiments substantiated this belief, and it was found that bile-acid combination of insulin is not destroyed by the stomach provided the latter is in postabsorptive state and the hydrochloric acid and ferments are neutralized. When such an insulin preparation is administered by mouth, it is absorbed as fast as from subcutaneous administration. The author claims that among the many combinations of insulin preparation with various derivatives of cholic acid, the most potent is the one which is prepared in a "special

manner" ("nach einem besonderen Verfahren") and is an addition product of insulin and of desoxycholic acid. The solution of this preparation is heat stable and can be boiled and sterilized. When it is administered subcutaneously it acts as does the usual commercial preparation. In order to neutralize the acid and fermented contents of the stomach, 2 grams of magnesium sulphate are administered twenty minutes previous to the administration of the insulin preparation. Following the oral administration of the insulin preparation to diabetic patients, the blood sugar falls, but slowly, and this fall may last as long as ten hours. If the administration of insulin is followed by the administration of food, the effect of the insulin becomes more prominent. The author therefore claims that orally administered insulin reaches its maximal effect if the "gastrointestinal reflex" is active. The effect of the preparation on diabetic patients is different from that on normal subjects. In severe cases of diabetes, the effect is apparently more pronounced than in mild cases. Apparently for each case there is an optimal dose for oral administration. Doses above this optimal amount exert no toxic effect. The therapeutic effect of this insulin preparation on the general condition of the patient is identical with that of the subcutaneous insulin therapy, according to the author's statement. The author does not claim that his observations solve the problem of the oral administration of insulin. The main purpose of the publication is to combat the pessimism hitherto persisting in the problem of the oral administration of insulin.

The Oral Administration of Insulin to Diabetic Children.—OTROW (*München. med. Wchnscher.*, 1929, 38, 1584) reports her experiences with two diabetic children in using the preparation of insulin supplied by R. Stephan (see preceding abstract). She claims that the oral administration of insulin exerts a beneficial effect. The effect is slower than that after subcutaneous administration. The disappearance of sugar from the urine precedes the lowering of the blood-sugar level. Toxic effects are not noted.

The Treatment of Lung Abscesses by Direct Aspiration and the Injection of Nearsphenamin.—EDEL (*Med. Klin.*, 1929, 25, 668) reports upon most strikingly favorable results in a series of 8 cases with lung abscesses which were treated by means of aspiration of the abscesses through a needle passed through the chest wall. Following the aspiration the syringe is detached and a solution of nearsphenamin is injected directly into the cavity. The dose of nearsphenamin begins with 0.15 gm. and progressively is raised to a maximal dose of 0.6 gm., an interval of four or five days elapsing between successive injections. The injection is followed promptly by a clearing up of the feter, a general improvement in the patient's condition, a fall in the temperature and a very rapid evacuation and healing of the abscess cavity. A similar direct injection of nearsphenamin gives equally satisfactory results in the treatment of infected bronchiectatic cavities. The injection into this cavity, however, is made through the trachea after cocainization. This method of treatment lies between the true surgical procedure which has such a very high mortality and the very unsatisfactory medical methods which demand so long a period of time and yield such poor results.

PEDIATRICS

UNDER THE CHARGE OF

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Irradiated Foods and Irradiated Ergosterol.—BLUNT and COWAN (*J. Am. Med. Assn.*, 1929, 93, 1301) discuss these subjects rather completely, and inasmuch as newer products often find unexpected favor, it is necessary to register warning with those products in which unfavorable results have been seen from overdosage. These authors state that the enthusiasm for irradiated ergosterol must be tempered with caution, since like many other potent drugs large doses may be distinctly dangerous. This danger is comparable to that found with the glands of internal secretion such as the thyroid and pancreas; small doses of which are absolutely essential to normal physiologic activity but which in large doses act as violent poisons. This comparison is more vivid if the theory is believed that the vitamin D promotes calcification through the stimulation of the parathyroid gland. It has been shown that exceedingly large doses of vitamin D caused a rapid loss of weight followed by death within a short time not only in white mice but also in larger experimental animals, such as guinea pigs, rabbits, cats and dogs. As the result of overdosage these animals presented the same picture of definite and severe disease, namely, loss of appetite, rapid loss of weight, severe emaciation and marked decrease of vigor. Diarrhea often developed and death usually followed in a comparatively short time. Studies of the tissues after death showed enormous deposits of calcium in the walls of the bloodvessels and the vital organs such as the heart, stomach and kidney. This has been taken to indicate that there was stimulation of calcification to the point where the mineral was deposited in any and all kinds of tissue that would receive it whether or not it was needed or useful there.

The Comparative Value in Infant Feeding of Condensed, Fresh, Canned Natural and Whole Powdered Cows' Milk.—PEREZ (*Philippine Islands Med. Assn. J.*, 1929, 9, 265) informs us that the milk supply and its control in the Philippine Islands are still most primitive. The milk supply control is entirely overshadowed by the public health progress along other lines. He states that in many communities throughout the islands there are no dairy farms nor even milch cows. This results in a condition of extremely high cost, scarcity and even absence of a supply of satisfactory milk. There is the further difficulty of handling and preserving milk in the home because of the absence of refrigeration. Because of these conditions the pediatricians of the Philippine Islands are forced to employ canned-milk preparations for infant feeding, and the various brands of different forms of canned-milk products manufactured in United States and Europe are widely used and are freely sold in even the smallest shops in the smallest

villages. The author studied the safety and usefulness in a number of these preparations in infant feeding. Of the various products used by him, powdered whole cows' milk seemed to be most satisfactory. The results were very encouraging, especially when it is remembered that the preparation of the formulæ has been carried out by extremely ignorant people. Because of his results the author feels that powdered whole cows' milk is a solution for the problem of artificially feeding infants under conditions such as exist in the Philippine Islands. As it is in powdered form, it can be transported anywhere without refrigeration.

The Therapeutic Value of Irradiated Milk in the Treatment of Rickets.—WATSON and FINLAY (*Lancet*, 1929, ii, 704) confirm the claims of numerous German writers concerning the value of irradiated milk in the prevention and cure of rickets. They were of the opinion that irradiated milk should not be used as a complete substitute for good fresh untreated milk. They found in rickets in children between the ages of two and five years that excellent results followed when the milk was used in strength varying from 1 part irradiated to 2 parts non-irradiated up to equal parts of the two products. They feel that the cure of the disease is established more quickly and effectively as well as economically by the use of irradiated milk than by the use of various irradiated commercial preparations. They suggest that there are indications that irradiated milk may prove of great value in other disorders than rickets, especially those incident to pregnancy and lactation, the menopause, malnutrition, injuries and surgical diseases of bone and certain forms of tuberculosis.

The Determination of the Value of Serum in the Treatment for Meningococcus Meningitis.—WRIGHT, DE SANTIS and SHEPLAR (*Am. J. Dis. Child.*, 1929, 38, 730) found that the agglutination test did not give uniform results and was unreliable as a guide for determining the value of the certain serum against a specific strain of meningococcus. As other methods, such as the opsonic index and the complement-fixation test, have not been of proved value in this determination, therapeutic tests seems to be the only reliable method of determining the curative value of the serum against a specific organism. This test may result in fatality in the treatment of a series of cases. When a patient with a meningococcus meningitis fails to respond to treatment there is no justification for the conclusion that the strain of organism met is resistant to serum therapy; but the only justification is the conclusion that the serum used was not specific for that organism, and it becomes necessary to seek an effective serum. There appeared to be a loss of specificity against a certain strain of meningococcus when too large a number of strains have been used in the production of a polyvalent serum. A single intraspinal injection of 20 cc. of an effective antimeningococcus serum in each twenty-four hours proved adequate. Potency of the serum rather than frequency of injections seemed the essential factor for successful treatment. It is emphasized that the quantity of serum administered should usually be less by at least 3 or 4 cc. than the quantity of spinal fluid withdrawn. They also advised the administration of antimeningococcus serum in the cisterna magna when there is evidence of blockage in the spinal canal.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Nonspecific and Malarial Therapy in Neurosyphilis.—REESE (*Am. J. Syph.*, 1929, 13, 348) reviews the therapy of paresis, mentioning particularly the use of tuberculin, vaccine therapy and the use of nonspecific agents, that is, peptone, milk turpentine, aolan, and sodium nucleinate. Including the more recent reports in the therapeutic use of intermittent fever and rat-bite fever, the author believes that the best results are obtained with malarial therapy, particularly when supplemented by tryparsamide, mercury and iodids. Reese uses 6 to 10 cc. of infectious blood by intravenous inoculation for the average patient. Reinoculations after eight to fifteen months are most successful when the infectious blood is introduced intramuscularly as well as intravenously. Determination of blood groups in donor and recipient is advisable. After the patient has had from three to six chills, the author routinely uses such cardiac stimulants as camphorated oil or caffeine. Digitalis is avoided because of the bradycardia it may induce in conjunction with the later quinine. Modifying the severity of the general reaction, small doses of quinine are given. This procedure, it is hoped, will have a tendency to lessen the mortality rate. Indications for interruption of the malarial infection are poor physical condition, intercurrent disease, jaundice, nasal or oral hemorrhages and an increase of the blood urea (O'Leary's urea-nitrogen index). Organic metabolic diseases, circulatory diseases with high-systolic and low-diastolic pressure and chronic alcoholism are contraindications to malarial therapy. Aortitis or myocarditis without decompensation is not always a contraindication. Reese comments on the complexities of the factors operating in malaria therapy. A disturbance of the vegetative reflexes results in the emigration of the leukocytes toward the seat of an inflammation, and the author visualizes a similar activity in and about the inflammation of the nervous system. If the effect obtained in paresis is due to increased omnicellular activity, such a hyperactivity is the result of altered vasomotoric equilibrium accompanying or following the malarial chill and not the result of fever or some questionable antibodies. The chills, by altering the vegetative balance of the vasomotor system, with resulting dermatographism, peripheral leukopenia and a drop in blood pressure, produce a renewed and intense activity in areas of chronic inflammation. The majority of the cases treated were paresis. The author points out that the pathology in tabes dorsalis is so different from that of paresis

that it would be difficult to see how malaria could possibly change tract degenerations and their clinical manifestations. Improvement was obtained in 42 per cent of the men and 46 per cent of the women. Fair results were obtained in 23.8 per cent and a mortality rate of 4.6 to 8.5 per cent was encountered. The author defines a successful result in the therapy of paretics as a restoration of mental capacity, the control of the emotional sphere and a good insight into ethics and law. The ability to resume a lucrative occupation is the best gauge of such results. The writer warns against the malarial remittent parietic, however, as one who often lacks quick and sound judgment and is apt to err suddenly, and as such is not fitted for positions of responsibility which might make these exactions.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Uterine Retrodisplacement.—In the treatment of uterine retrodisplacements the pendulum has been swinging widely. A decade or two ago practically every retroverted uterus was given the benefit, if such it may be called, of a suspension operation. Such operations were extremely popular and there were few gynecologists worthy of the name who did not have a pet modification of some operation if they were not clever enough to have an operation named after them. It was gradually determined that many of the patients who had been subjected to such surgery were not relieved of their symptoms so that the reactionary element in the profession declared that very few suspension operations were ever indicated. As is usually the case, the proper attitude toward this subject is probably a middle course, using great discretion in the selection of cases. In an experience of twenty-seven years as head of the Department of Obstetrics and Gynecology in the University of Michigan Hospital, PETERSON (*Ohio State Med. J.*, 1929, 25, 541) has records of 31,000 cases of all kinds to draw upon for information. Concerning movable retroversion he states that those who deride any treatment of such uteri on the ground that no symptoms arise from them are quite as wrong as those who claim that all such cases are cured by operation. Of course many of the symptoms formerly thought to be due to retroversion are in reality due to muscle strain dependent upon faulty posture, mechanical spinal faults and disease of the joints. No longer is it permissible to study the pelvis alone and ascribe all aches and pains in the back, groins and legs to pelvic lesions. One must have a working knowl-

edge of symptoms which may be expected from certain skeletal and postural defects. There is nothing mysterious about the technique of such examinations. One does not have to be a specialist to make a differential diagnosis between backache caused by faulty posture, sacroiliac strain and pelvic disease. In his clinic every patient is studied not only gynecologically but for a possible explanation of her symptoms because of faulty posture and skeletal defects. He believes that the man who is willing to assume the responsibility of an operation for a retrodeviated uterus ought to be willing to devote enough time to the study of his patient to determine whether her symptoms are due to faulty uterine position, intrapelvic disease or to faulty posture with resulting ptosis and muscle strain, subluxation of the sacroiliac joints or actual disease of the spine or pelvic girdle. Without a working knowledge of how to determine the conditions which may give rise to certain symptoms he is incompetent to determine whether or not the patient should be operated upon for her uterine condition. He does not assume that the position of the uterus is of no consequence, but in itself it may or may not be producing symptoms. If the case is suitable for operation he has found the Gilliam operation to be the most satisfactory technique.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Facial Paralysis Associated with Acute Otitis Media.—The appearance of a facial paralysis in the course of an acute otitis media is very uncommon. Less than 1 per cent of all otitic suppurative processes present involvement of the facial nerve. Most facial paralyses are of peripheral origin—presumably due to such compressive factors as congestion, hemorrhage or mild inflammatory exudates within or without the nerve sheath. In reporting 3 personally observed cases, MORWITZ (*Ann. Otol., Rhinol. and Laryngol.*, 1928, 37, 1263) concludes from his experience and from a study of the literature that the prognosis in this type of case is very good, although disappearance of the facial palsy may be extremely slow; that the treatment of the facial paralysis is essentially that of the ear condition *per se*; and that the paralysis as a complication is not necessarily an indication for operation. Inasmuch as the peripheral fibers of the facial nerve show a marked tendency to regenerate, complete disappearance of the paralysis usually occurs in from ten days to six weeks. In prolonged cases, physiotherapy (galvanism) should be instituted.

Experiences Concerning Mucosus Otitis.—In a series of bacteriologic cultures from 288 operative cases, VOGEL (*Ztschr. f. Hals-, Nasen- u. Ohrenh.*, 1929, 22, 357) found hemolytic streptococci in over one-half of

the cases and *Pneumococcus mucosus* (also known as *Pneumococcus III* and *Streptococcus mucosus*) on 52 occasions (18.2 per cent). An analysis of the clinical data of 50 of the "mucosus" cases showed that 40 were adults, and 10 were children. Twenty-five of the adults exhibited a typical picture of mucosus otitis, pursuing a progressive course and presenting but few symptoms. The duration of the infection was much shorter in the young than in the adults. In some children postauricular swelling was the first outstanding manifestation. The tympanic membrane was not perforated in 5 instances. Intracranial complications were noted in over one-half of the 50 cases. Meningitis occurred eleven times. The mortality was 24 per cent, and was much higher than the 7 per cent resulting from a mixed flora, even when *Pneumococcus mucosus* was included. The author could not substantiate Steutz's claim that this organism has a predilection for the normally pneumatized mastoid cells. In the aged, the asthenic and in certain diabetics, a pathologic process similar to the one produced by "mucosus" can be caused by other bacteria—notably, *Streptococci*, *Bacillus friedländer* and *Bacillus proteus*.

Tuberculosis of the Middle Ear.—Asserting that aural tuberculosis has not been sufficiently recognized in the past, due to the belief that it is a rare disease and to the difficulties of diagnosis with the older laboratory methods, COX and DWYER refer to a previous report (*J. Laryngol., Rhinol. and Otol.*, 1916, 31, 288) wherein, of 32 children with chronic otorrhea, cultures revealed the presence of *Bacillus tuberculosis* in 5 (15.6 per cent). In the present communication (*Arch. Otolaryngol.*, 1929, 9, 414) the authors add 10 additional cases of aural tuberculosis from the discharges of whom the *Tubercle bacillus* was isolated and cultivated by the use of sodium hydrate in conjunction with Miller's medium—the basis of which is an extract of the lymph glands and spleen of laboratory animals. In discussing the various features of otitic tuberculosis the authors mention that the prognosis is not necessarily unfavorable, although the tendency to osseous necrosis, facial paralysis, labyrinthitis and tuberculous meningitis should be remembered; that in children the infecting agent is often of the bovine type, coming from cows' milk; that further investigation is needed to prove the true value of heliotherapy; and that "appropriate local, general and climatic treatment combined in suitable cases with injections of tuberculin, offers the best hope of a cure."

Spectrographic Examination of Pellagrins' Sera.—SCOTT, TURNER and MAYERSON (*Proc. Soc. Exp. Biol. and Med.*, 1929, 27, 27) write that exposure to direct sunlight produces or intensifies the erythematous eruptions on the parts of the body exposed to the sun. Why this occurs is not known, but it has been suggested that it may be due to hemato-porphyrin in the blood. To determine this point; whether or not hemato-porphyrin was present in the serum, the sera from 13 patients with active pellagra were examined with a Hilger quartz spectrograph. They recite in their article the technique of the examination. As a result of their study they are able to state definitely that there is no difference between the spectra of normal and pellagrous sera and that hemato-porphyrin is not present in the circulating blood of the pellagrous individual.

RADIOLOGY

UNDER THE CHARGE OF

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The Significance of Small Intestinal Stasis.—KORNBLUM (*Radiology*, 1929, 13, 17) has been able to distinguish between two main groups of cases showing small intestinal stasis. The first is that group which has received considerable attention from roentgenologists and which manifests what is commonly spoken of as "ileal stasis." The characteristics of this group consist primarily in a delay in the advance of the head of the opaque meal. At six hours this usually has extended only as far as the cecum, and occasionally the entire meal is in the terminal ileum, the loops of which are not distinguishable except by palpation, and are then often found to be of larger caliber than normally. Some of the more common causes are colonic stasis, adhesions, neoplasms of the large bowel, and external pressure from abdominal and pelvic tumors. Probably the most important single factor causing ileal stasis is adhesions resulting from inflammatory conditions of the appendix. The second group of cases showing small intestinal stasis differs markedly from the first. The advancement of the head of the opaque column is variable. The most striking feature is the variety of forms assumed by the intestinal shadow. The opaque material, while seen occasionally as one continuous shadow, is more frequently broken up into segregated loops, the masses varying in size, shape and caliber. Quite as significant is the finding of gas distended loops. Causes of stasis in this group comprise adhesions, subacute and chronic peritonitis from cholecystitis or perforated ulcer, ascites, tuberculous peritonitis, primary lesions of the small bowel affecting its lumen, metastatic malignant lesions, morphin, and purely nervous causes including fear. Kornblum particularly emphasizes the frequency of stasis from malignant metastasis to the peritoneum, and the low-grade peritonitis of a nonmalignant nature which commonly occurs with ulcerative and infected cancers of the stomach and colon.

Evaluation of Heliotherapy in Tuberculosis.—WATSON (*Arch. Phys. Therap., X-ray, Radium*, 1929, 10, 252) considers that heliotherapy is by no means indicated in all cases of tuberculosis. There are many tuberculous patients who should never use it. In general, direct sunlight is indicated in cases of extrapulmonary tuberculosis and contra-indicated in cases of pulmonary tuberculosis. For no type of tuberculosis is heliotherapy a cure; but often, especially in the extrapulmonary cases, it is a very valuable, or even necessary, aid. Since it is not in itself a cure, heliotherapy should never be used to the exclusion of the

usual standard therapeutic measures. Never should it be forgotten that the direct rays of the sun are extremely powerful, and that, carelessly administered, they can effect great harm. Direct sunlight, in the same amount, affects patients differently—more differently, especially in the beginning of its use, than almost any other remedy. Obviously, therefore, it must be used, in every case, not according to any hard and fast rule, not according to any theoretically predetermined dosage, but according to the individual reaction. Heliotherapy is of the greatest value, and may be practised with the least chance of doing harm, in pure extrapulmonary tuberculosis, that is, in the so-called surgical tuberculosis without pulmonary lesion. It is of great value in extrapulmonary tuberculosis with coincident pulmonary lesion; but in giving it here one must be far more careful than in the uncomplicated surgical type, particularly as regards exposing the thorax. It is of great value in hilum gland tuberculosis, and in this type should invariably be used. It is of some value in some cases of the proliferative type of pure pulmonary tuberculosis; but here it must be employed with the greatest caution, lest it transform a favorable, stationary, or healing lesion into a rapidly progressing and fatal one. It is virtually never of value, and is often positively harmful, in the exudative type of pure pulmonary tuberculosis, as well as in all acute types; and in such cases, therefore, it ought never to be used.

Treatment of Hemorrhage from the Nonmalignant Uterus.—NORSWORTHY (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 336) emphasizes careful selection of cases. Adolescent hemorrhage at the beginning of the menstrual function with irregular daily bleeding, if mild, may be corrected by general attention, and ovarian, thyroid or pituitary extracts. Radium should not be used until these fail. In epimenorrhea (too frequent menstruation), menostaxis (the prolonged type), and menorrhagia from a small or normal-sized uterus may be treated with radium. Menorrhagia from an enlarged uterus, in the absence of infection, calls for curettement. Menorrhagia from an enlarged fibrous uterus, even in the young woman, when found to be the result of infection, will respond completely to no other treatment than removal of the uterus. It must not be forgotten that radium is a dangerous agent when used in or around the pelvis of young women. It should be used in girls or young women only in small doses, and not until simpler methods have failed. Routine irradiation in submucous fibroids is contraindicated; operative removal is the treatment of choice. In bleeding associated with adnexal disease, surgical operation is the safest treatment. In pernicious hemorrhage during gestation the spleen and thyroid gland should be irradiated. Contraindications to full doses of radium, in the absence of malignancy, are: (1) cachexia out of proportion to the loss of blood; (2) pelvic or peritoneal infection; (3) tumors rapidly increasing in size; (4) pedunculated and calcifying tumors; (5) submucous tumors which so distort the uterine cavity that easy introduction of the radium applicator is prevented; (6) age, while an important factor at either extreme, does not contraindicate its use; radium is a valuable agent in checking hemorrhage in young girls and elderly women do not react badly to it.

NEUROLOGY AND PSYCHIATRY

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A New Sign of Cerebellar Disease.—WERTHAM (*J. Nerv. and Ment. Dis.*, 1929, 69, 486) finds that diadochokinesis, which is essentially an inability to perform rapidly alternating movements, can be distinguished from the ability to perform rhythmic movements correctly regardless of speed. This latter ability, he designates rhythmokinesis and has devised a test for its disturbance which enables one to make a graphic record of the changes. The disturbance of this ability, he designates as arrhythmokinesis. He tested a group of cases, including most of the varieties of conditions in which adiadochokinesis can occur, and found that arrhythmokinesis did not coincide with the occurrence of adiadochokinesis, although the speed of the performance of rhythmic movements in adiadochokinetic cases was often slower than normal. Since all of the cases showing arrhythmokinesis had definite involvement of the cerebellum, he believes that this function is more closely related to cerebellar disease than is diadochokinetic ability. He presents 5 cases in which the disturbance was present and in which the cerebellum was definitely involved, all confirmed by operation. He assumes that the mechanism is fundamentally the same as that underlying the adiadochokinesis of cerebellar disease and considers the disturbance to be primarily irregularly in amplitude of action currents, their continuation long after the mechanical movement has stopped, and considerable lack of synchronous relations between flexor and extensor action currents.

Contribution a l'Etude Anatomo-clinique de l'Amyotrophie Charcot-Marie.—MARINESCO (*Revue Neurologique*, 1928, 2, 543) reviews the history of amyotrophy of the Charcot-Marie-tooth type and presents a case with pathologic studies following death. The patient was thirty years of age and had the first manifestations of his illness at the age of eighteen years. The progress of the disease had been irregular. At autopsy, the author found grossly the degeneration of the muscle group involved in the legs and arms. Histologically, there was a degeneration of the motor fibers in the peripheral nerves with changes in the anterior horn cells similar to those usually found after section of a nerve. They also found in the cord a degeneration of the tracts of Burdach and Goll. This degeneration was scarcely apparent in the sacral region. It was increased slightly in the lower lumbar segments and in the upper segments practically obliterated the posterior tracts. In the thoracic region a similar condition held but in the lower cervical region the lesion

was less diffuse, affecting only those central fibers belonging to the tract of Goll. In the upper cervical region both Goll and Burdock tracts were affected. In the spinal ganglia he found residual nodules and other changes suggesting a reaction similar to those found in posterior column, sclerosis generally. The muscles showed histologically changes which appeared to be of an autolytic character. On the basis of these findings the author considers that the lesion in the Charcot-Marie-tooth type of amyotrophy is primarily a lesion of the axones of the motor and sensory nerve cells showing itself by changes in the muscles and anterior horn cells secondary to the degeneration of the motor axones; and by the atrophy of the posterior columns and changes in the spinal ganglia which constitute direct manifestations of the sensory lesions.

An Investigation of a "Mind-reading" Horse.—RHINE and RHINE (*J. Abnormal and Social Psychology*, 1929, 23, 449) present a study of Mrs. Fonda's horse, Lady, who was reputed to have telepathic powers. They present in detail a number of experiments that were carried on over a period of a year. In many of these experiments the controls were checked as carefully as is possible in such experimentation. The controls were aimed at ruling out any ability on the part of the agent to signal to the percipient either consciously or unconsciously, or for unconscious suggestions to be made by observers. They notice especially the sleepy, rather apathetic, appearance of the horse during the demonstrations and the ability of the horse to move directly to the required object, and so forth, in the tests. The passivity of the horse, they state, could be deepened so much as to render her apparently motionless and almost asleep. She could be awakened at any time by a sharp command or a touch of the whip and would become quickly a normal, active colt again. They conclude that their experiments are sufficiently well controlled to leave only an explanation of telepathic communication to account for the results.

On Myasthenia Gravis.—QUERIDO (*J. Nerv. and Ment. Dis.*, 1929, 69, 522) presents a case of myasthenia gravis studied both clinically and pathologically. His case is quite typical, the characteristic pathologic findings in the muscles being present. However, he found that the cellular infiltration about the smaller bloodvessels contained leukocytes, lymphocytes, plasmatic cells, fibroblasts and ripe fibrous tissue with traces of hemorrhage, and that the walls of the vessels running through such foci were infiltrated with the same types of cells. He offers the hypothesis that myasthenia gravis is a general vascular disease defined pathologically as a perivascularitis chronica proliferans. Since the pathologic preparations in his cases correspond fairly closely with those described by other authors he feels that in former pathologic studies the authors have been misled by Weigert's original communication regarding the presence of lymphocytes. He has compared his preparations with microphotographs occurring in the literature, but since all of these were of low-power magnification it was impossible for him to determine the actual character of the cells in the foci. If the hypothesis is correct he believes that it will explain the great variety of manifestations which occur in this disease.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Structural Changes of the Liver in Pernicious Anemia. A Contrast Between Relapse and Remission.—METTIER (*Arch. Path.*, 1929, 8, 213) studied comparatively the histopathology of the liver in 20 patients with pernicious anemia not treated with liver substance who died during relapse with that in 5 patients treated with liver who died from intercurrent disease while the anemia was in partial or complete remission. The most marked difference was noted in the Kupffer cells, which were of normal size in remission but showed pronounced hypertrophy during relapse. Desquamation of Kupffer cells and phagocytosis of erythrocytes occurred in both stages but was not more marked than in other severe anemias or in infectious diseases. Siderosis which was marked in the liver cells and moderate in the Kupffer cells during relapse was greatly lessened during remission. Although megakaryoblasts occurred free in the sinusoids of the liver in the patients who died during a relapse, hepatic hematopoiesis was not found in any of the 25 organs.

Histologic Changes in the Spleen in Early Congenital Syphilis with Special Reference to the Origin of Anemia in this Disease.—WATSON (*Arch. Path.* 1929, 8, 224) reports the histologic appearance of the spleen in 4 cases of congenital syphilis, 3 of which presented severe anemia during life. The endothelial cells lining the sinusoids as well as the macrophages free in their lumina contained both nucleated and mature red blood cells in addition to large amounts of hemosiderin. Normoblasts were of frequent occurrence, but there were no other signs of myeloid metaplasia. In 2 cases examined, the anemia was of a regenerative type while in one the presence of bilirubinemia was associated with an indirect van den Bergh reaction. The author believes that these observations, together with the histologic changes in the spleen constitute evidence that the anemias were hemolytic and imply that the spleen plays an important rôle in their origin.

The Identity of Human Leprosy and Rat Leprosy.—There has been a very great difficulty in advancing the study of leprosy, because of not having the benefit of animal experiments. The work of WALKER (*J. Prev. Med.*, 1929, 3, 167) has shown that the microorganism of leprosy appears in many morphologic forms and that Hansen's lepra bacterium is a tissue stage of this organism which may appear as coccoid, streptococcoid, diphtheroid, rod and branching filaments in

cultures and that it belongs to the genus *Actinomyces*. The author believes that human leprosy is primarily a soil infection with this facultative parasite, probably through wounds in the skin. The occurrence of a similar disease in the rat stimulated WALKER and SWEENEY (*J. Prev. Med.*, 1929, 3, 325) to study this disease, and they have been able to clarify many of the obscure facts relating to human leprosy. They emphasize the balanced relation existing between parasite and host, and their work helps to explain the spontaneous decline of leprosy under improved economic and hygienic conditions as well as anticipating the appearance of sporadic cases and a number of other previously confusing observations. A very important part of their evidence supporting the identity of these two diseases was the discovery of the high incidence of latent infections among rats, and suggests its probable existence in man.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Distribution of Endemic Typhus (Brill's Disease) in the United States.—MAXCY (*U. S. Pub. Health Rep.*, 1929, 43, 3084) reviews briefly the history of typhus in North America and shows that cases have been reported from 16 states in the period 1915-1927. None of the cases was traceable to importation. The cases noted above do not include the many from the southeastern states. Georgia alone reported 127 cases in 1927. Generally speaking, the disease is now limited to the Atlantic seaboard and the Piedmont region adjacent. The report concludes with the following paragraph: The limitation of this disease geographically does not seem to be explained satisfactorily on the basis of direct person to person transfer or through the intermediation of the louse. Some agency other than man and his own parasites would appear to be responsible for the preservation of the virus. This agency, be it insect alone, or an insect which feeds upon some host other than man, must be correspondingly limited in its distribution, or at least its capacity for acting as a vector to man must be so limited.

Trachoma in the State's Health Program.—MOSSMAN (*U. S. Pub. Health Rep.*, 1928, 43, 449) gives a brief historical review of trachoma work in the United States, pointing out that the first surveys were made in Kentucky and that these have been followed by curative and pro-

phylactic work, especially in West Virginia, Tennessee, Arkansas and Missouri, in all of which states the disease is particularly prevalent in certain sections, some communities being very heavily infected, while other communities are free, or relatively free. The situation in Missouri has been especially emphatically demanding attention because, since 1922, that state furnishes financial relief to blind persons to the extent of \$300 per year per person; about 20 per cent pensioners are blind as a result of trachoma, and this feature of the blindness is costing the state about \$200,000 per year in direct payments, without considering the economic loss in medical treatment and the loss of time of the individuals. In many communities the trachoma work is giving the people their first acquaintance with modern public health work of any sort. This leads either to the installation of full-time health department organizations, or to the amplification of the activities of organizations already in existence. The trachoma hospitals thus have four functions, as follows: (1) Clinical treatment of trachoma for the purpose of preventing damage to sight and of stopping the patient from being a spreader of the disease. Field surveys have shown that the results of treatment. (2) Study of the disease itself. We are constantly on the alert for improved methods of diagnosis and treatment. Although nothing revolutionary has been discovered, we believe that we have made substantial improvements both in accuracy of diagnosis and in effectiveness of treatment. (3) Education of patients in personal hygiene and disease prevention. Patients admitted to these hospitals receive careful treatment for trachoma and also instruction in personal hygiene, health, habits and general health education. They are enabled to go home relieved of their disease and trained to some extent at least to live in a clean, health-promoting manner. (4) Centers for field work. Trachoma surveys are made in the surrounding territory by the staffs of the hospitals, by means of examination of school children, and by community clinics. During recent months it has become the policy to have field clinics arranged by a Public Health nurse for the special care of trachoma cases who have been hospitalized or who, for some reason or other cannot, or do not need to, be given hospital treatment.

The Minimal "Chlorine Death Points" of Bacteria. I. Vegetative Forms.—TONNEY, GREER and DANFORTH (*Am. J. Pub. Health*, 1928, 18, 1259) found that a large majority of the vegetative types of organisms considered to be of sanitary importance in connection with water supplies, milk supplies, dish washing, bottle washing, and general disinfection, whether of intestinal or respiratory origin, are killed in a few seconds by rather small doses of free chlorin, when exposed in a suspension containing no organic matter or other substances that react with or absorb the chlorin. This was true for temperatures ranging from room temperature to within a few degrees of the freezing point of water. The amount of chlorin required to kill most of the intestinal pathogens studied under these conditions was 0.1 p.p.m., with the greatest destruction of the organisms occurring within the first fifteen seconds of exposure. The same amount of chlorine destroyed most of the pathogenic types of respiratory organisms tested. In each group, however, there were individual strains which were more resistant to

chlorine than the others, requiring more than 0.1 p.p.m. to accomplish their destruction. In the intestinal group of organisms, the most resistant type encountered was *Bacillus coli*. In the group of respiratory origin, three strains of hemolytic streptococci, out of 24 strains tested, required larger quantities of free chlorin for their complete destruction. All the resistant strains of streptococci were killed by 0.25 p.p.m. in fifteen to thirty seconds. It is probable that the apparently higher resistance of the streptococcic strains is due to the larger number of organisms used in order to secure consistent growths. From the standpoint of resistance to chlorin, *Bacillus coli* stands out among the organisms tested as the most suitable for use as an index of the effectiveness of chlorin disinfection. The requisites of such an index organism are: (1) that it be as resistant as, or somewhat more resistant to, free chlorin than the pathogenic organisms which are to be destroyed; (2) that it grow readily on simple media; (3) that it be readily recognizable by simple routine tests. From the standpoint of availability, rapidity of growth, and ready detection, *Bacillus coli* offers superior advantages as an index organism, and it is our feeling that the consistent absence in a menstruum after chlorine disinfection is valuable evidence of the destruction of the pathogens here studied. On the whole the experiments appear to furnish a satisfactory theoretical basis for the current practice of relying on the consistent destruction of *Bacillus coli* in water as a criterion of effective chlorination, and that they may also justify a more general application of the same criterion to the other type phases of chlorine disinfection now being developed, such as the washing of milk bottles and equipment and the washing of dishes and eating utensils.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 18, 1929

On the Oxidizing Power of Oils and Its Modifications Under the Influence of Oligodynamic and Radioactive Agents.—JAYME R. PEREIRA (from the Department of Pharmacology of the S. Paulo Medical Faculty, S. Paulo, Brazil). The oxidizing power of various vegetable, animal and mineral oils was determined by the following technique: 5 cc. of the oil were transferred to an Erlenmeyer flask, to which were also added 2 cc. of a 20 per cent solution of acetic acid and 28 cc. of a 10 per cent solution of potassium iodid. This mixture was violently shaken for a few minutes and allowed to stand in a dark closet for twenty-four hours, at the end of which time the free iodine was determined, using a $\frac{N}{100}$ solution of sodium thiosulphate in presence of starch. The results were expressed in terms of cubic centimeters of the thiosulphate solution used.

It was found that mineral oils are devoid of any natural oxidizing power. In regard to the vegetable and mineral oils, they presented enormous variations, not only among the different species, but also among the specimens of the same species. This may be due to the different methods employed in their preparation and, in all probability, to their adulteration for commercial purposes.

One specimen of almond oil (Escoffier Fils—Grasse, France) showed a very high oxidizing power (2.3 cc. of thiosulphate solution), while a specimen of castor oil (Carlo Erba—Milan, Italy) did not show any power at all.

Under the action of silver (porcelain rings covered on the outside and inside with a coat of metallic silver) both the almond oil and the cotton-seed oil showed alternate phases of reduction and oxidation, that is their oxidizing power was periodically decreased and increased during the exposure to the action of silver. Practically the same results were obtained with paraffin oil and distilled water, which have no natural oxidizing power. In this case both these two substances acquired oxidizing power which showed then the same fluctuations spoken of before.

Under the action of "radia" (an emanogenic substance used to radio-activate drinking water) similar results were observed.

The relationship between the oxidizing power and the antirachitic potency of certain oils which has been previously shown by several investigators in connection with ultraviolet irradiation, suggests that experiments must be done in order to determine whether the oligodynamic and radioactive agents are also able to increase the antirachitic potency of the oils or not. This will be done in future experiments.

Relation of Monocytes of the Blood to the Tissue Macrophages.—ELIOT R. CLARK and ELEANOR LINTON CLARK (from the Laboratory of Anatomy, University of Pennsylvania). A portion of the life history and many of the morphologic characteristics and reactive powers of the tissue macrophages have been studied by observation, with highest microscopic magnifications, of living cells in the transparent tails of Amphibian larvæ. Individual cells were followed by uninterrupted observations of four to thirty-six hours' duration.

The differentiation of early mononuclear wandering cells from a strand of primitive mesoderm located just ventral to the developing notochord was followed in Axolotl larvæ, at a stage before the first appearance of vascular endothelium or of blood cells in the tail. The change of such early wandering cells, following phagocytosis of various substances, into typical large pigmented macrophages was observed.

The tissue macrophages were found to be actively migratory and exceeding phagocytic and to undergo amazing transformations in shape and size. Macrophages were also found to be the most resistant cells present in the region studied. They were never seen to die even in cases of degeneration of or of injury to large surrounding areas, involving all other types of cells present.

The permanent transformation of macrophages into any other form of blood or tissue cell was never observed.

When small amounts of cream were injected into the extravascular tissue of the tail typical pigmented macrophages migrated toward the

injected globules and actively engulfed them. In addition, smaller, clear mononuclears moved directly toward the injected cream and joined the macrophages in the active phagocytosis of the globules. Cells filled with cream globules remained near the injection site for several days, during which time the ingested globules became smaller and the cells became more pigmented. After several days all of the cells of the group were similar in appearance, that is, they all resembled typical macrophages.

Larger injections of cream into the tissue stimulated the migration of leukocytes from the vessel. Monocytes then wandered toward the cream globules and joined the macrophages and clear mononuclears from the tissues in ingesting the cream. Polymorphonuclears and lymphocytes migrated also, but their reaction toward the cream was so slight as to be negligible.

In order to distinguish positively between cells which have migrated from the blood and cells from the tissue carmin granules were injected into the blood stream and their phagocytosis by monocytes was followed in the living. Circulating monocytes retained the carmin for two weeks or longer. Using tadpoles whose circulating monocytes were marked with carmin, cream was then injected into the outside tissue in amounts sufficient to stimulate emigration from the vessels.

In addition to migration toward the injected cream of (unmarked) macrophages and clear mononuclears from the tissues, carmin-containing monocytes were seen to migrate from the bloodvessels toward the cream and to take part in its phagocytosis. The carmin-marked cells were followed for two weeks and were found to display all the properties of appearance, movement and phagocytic powers characteristic of typical macrophages.

From these experiments it appears that the monocyte and the macrophage are two phases of the same cell, and that after the first differentiation of early tissue mononuclears, the supply of tissue macrophages is added to by the migration of monocytes from the blood stream.

Regarding the source of the monocytes in the blood, our observations supply no data. No proliferation of endothelium to form free cells was seen.

The Influence of Irradiated Ergosterol on Thyroparathyroidectomized Dogs.—J. H. JONES, M. RAPAPORT and H. HODES (from the Department of Physiologic Chemistry, School of Medicine, University of Pennsylvania). It has been demonstrated¹ that dogs given a preoperative treatment of cod-liver oil live for several weeks after the removal of the parathyroid glands, although the level of serum calcium be low. This is unusual, as dogs from which the parathyroids have been removed usually die within two to five days following the operation. Unpublished data show that irradiated ergosterol acts in a similar manner. Hess, Weinstock and Rivkin² and Greenwald and Gross³ have reported negative results from the administration of large doses of ergosterol after the glands have been removed. Any postoperative treatment must of necessity act rapidly if it is to prevent the death of an animal which would otherwise die in a few days. On the other hand, if the length of life is increased by treatment before operation, the chances.

for beneficial postoperative treatment are enhanced. With this in mind dogs were given treatments with ergosterol before operation. After the concentration of calcium fell to a low level following the removal of the glands ergosterol was again given in large amounts. Brief description of the experiments follows: Three dogs were given from 10 to 20 mg. of irradiated ergosterol daily for varying periods of time before the removal of the glands. The treatment was discontinued at the time of the operation. The concentration of serum calcium gradually fell until it reached 5.37, 6.01 and 7.34 mg. per 100 cc., respectively. At these points ergosterol was given in quantities of 50 mg. daily. The calcium rose to 20.1, 17.75 and 15.75 in two, fourteen and three days respectively.

Having received such striking results with these animals, it was thought advisable to try the postoperative effect of ergosterol on animals which received no treatment before operation. The parathyroids were removed from 4 dogs which received no preoperative treatment. The concentration of calcium fell within two days to 5.78, 5.45, 5.85 and 7.16 respectively. The first 3 developed tetany and were given milk in addition to 50 mg. of ergosterol daily. The first dog of this series vomited everything that was given and died on the ninth day after operation. The serum calcium on the seventh day was 5.78. The other 2 that were given milk retained it and in a few days began to eat the regular ration, at which time the milk was discontinued. The serum calcium of these two dogs increased to 17.6 in ten days and 47.27 in fourteen days respectively. Fifty milligrams of ergosterol were given daily to the remaining dog, starting with a calcium level of 7.16. No milk was given this animal. On the fourteenth day the calcium was 21.6.

Hemoglobin determinations showed no marked change in blood concentration. The inorganic phosphorus was also followed without any noteworthy results, except in the case of the dog with the extremely high calcium. When the calcium concentration was highest the phosphorus was 19.05 mg. per 100 cc. of serum. These experiments would indicate that ergosterol does not cause the increase in calcium of the blood by stimulating the parathyroid glands.

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Some In Vivo Uterine Responses in the Unanesthetized Rabbit.—S. R. M. REYNOLDS (from the Department of Physiology, University of Pennsylvania and the University of Chicago). Despite the many studies of uterine activity heretofore reported, none have been made *in vivo* in the unanesthetized chronic animal under conditions such that graphic records of the activity might be obtained. At the suggestion of Dr. M. H. Friedman, this was undertaken. A uterine fistula was made aseptically in a nonpregnant rabbit doe by transection of the vagina 1 to 1½ cm. below the uterovaginal junction. The intact orifices of the uteri were then passed through a stab incision to the exterior

in the lower left abdomen. Records of uterine activity can be obtained from time to time in such preparations. For recording, an air-water system, consisting of a water-distended balloon connected through an adjustable reservoir to a Brodie bellows, is employed. While the unanesthetized animal is secured in a supine position, the balloon is placed $3\frac{1}{2}$ to 5 cm. within the uterine cavity, and from this records are obtained. Studies on several animals, extending from April to August, inclusive, show that there are marked variations in the type of activity obtained from time to time in the same animal. Thus, the uterus may be relatively quiescent; then within the space of several weeks it may exhibit a large rhythmical type of activity, while in a few weeks more the uterus may be inactive. It is possible that this change may be associated with variations in the sex cycle, but this was not tested. When pituitrin is intravenously injected an initial tetanus immediately follows which lasts three to five minutes. A period of *inactivity*, lasting from three to ten minutes, follows this. On the other hand, when pitocin (oxytocin) is injected there is *no* period of inactivity following the initial tetanus. If one administers pituitrin or pitocin at a time when the uterus is not spontaneously active, the uterus is refractory to the drugs, and responds only feebly. This is not the case in the excised uterine strip. Even though the fistula response may be small, nevertheless, it is characteristic for the two drugs respectively, as described above. The extent to which these results on the nongravid uterus may apply to the gravid uterus has not been determined, hence their applicability to the clinical use of these drugs cannot yet be estimated.

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ORIGINAL ARTICLES.

SOME PRESENT-DAY CONCEPTS IN NEPHRITIS.*

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Introduction. Our understanding of Bright's disease has undergone considerable change in recent years. Many things have helped to produce this change. Not the least amongst these is a better knowledge of the normal functions of the kidneys, to the development of which so much has been added by the methods devised by Prof. A. N. Richards of this University. Chemical studies of the blood and the body fluids, detailed histologic studies of diseased kidneys, the routine use of the blood-pressure machine and the ophthalmoscope, have added to our understanding of the kidneys, and master clinicians have taught us how to correlate histologic changes in the kidneys with symptoms which are the expression of abnormal function. As a result, we have got away from old concepts current among clinicians of the older generation. We do not speak now of chronic parenchymatous nephritis and of chronic interstitial nephritis, the latter of which, as some one has said, is neither interstitial nor nephritis. Especially, we have drawn away from the clinical use of purely gross anatomic descriptions. We do not care now whether a kidney is white or red, large or small. Instead we have developed new concepts, and it is the meaning of some of these newer concepts that I want to discuss: The concept of renal insufficiency, what we mean by uremia, by nephrosis, especially lipoid nephrosis, and the concept of malignant renal sclerosis.

* Read before the Piersol Anatomical Society of the University of Pennsylvania, December 7, 1928.

I. **Renal Insufficiency.** *Insufficiency of an Organ.* We say an organ is insufficient when it is unable to perform the function for which it exists, in a complete manner. We speak of myocardial insufficiency, of liver insufficiency, as we speak of renal insufficiency. An organ performs its functions under a variety of conditions. The normal heart supplies the necessary amount of blood to maintain an adequate flow through the capillaries when the individual is at rest and when he is performing heavy work. If the heart is unable to supply a sufficient amount of blood when the individual is resting, we say that the heart is totally or markedly insufficient. If the heart supplies the necessary amount of blood when the person is resting but is unable to supply it when he is doing work, we say that the heart is relatively insufficient, or insufficient to a certain degree. We measure in a rough manner the degree of insufficiency by the difference between that which we know a normal heart can do and that which the particular heart under observation is actually accomplishing. To be able to measure this difference we must know the limitations of the normal heart and the maximum capacities which it possesses.

Similarly with the kidneys. If we are to estimate the degree of inability on the part of the kidneys to function properly, we must know what the normal kidneys can do. Frerichs, who was the greatest clinical teacher of his time, prefaced his book on Bright's disease with the motto taken from Marshall Hall: "To become good and enlightened practitioners, we must become able physiologists."

The Function of the Kidneys. The kidneys are the chief excretory organs of the body. As such it is their chief function to excrete the waste substances of metabolism, which cannot, like carbon dioxide, be excreted through the lungs, and which are not excreted through the intestinal tract. These are the waste substances of protein metabolism, namely, urea, uric acid and creatinin. The excretion of these substances is one of the functions of the kidneys. Another function is to play a part in certain of the regulatory mechanisms in the economy of the organism. The organism attempts to maintain constant values for those substances which it needs in its economy, and for those processes to which it has become adapted in phylogenetic development. In the words of Claude Bernard, it attempts to maintain a constant internal milieu in contrast to the ever-changing external milieu. A part of this internal milieu is a constant water content of the organism, especially of the blood, which the organism attempts to maintain by means of a regulatory mechanism. This mechanism has for its effector organs the water depots of the body, chief of which are the skin and the muscles, and the kidneys which excrete the water. A large amount of water when taken into the alimentary tract is soon absorbed from there into the blood stream. The blood is diluted temporarily and the water soon passes into the water depots, from where it is gradually

returned to the blood stream. Within one-half to three-quarters of an hour after the intake of the water, the kidneys begin to eliminate the excess of the ingested water. This whole mechanism is presided over by a regulatory center, and sufficient evidence is accumulating for the definite localization of this center in the hypothalamic region of the brain. The studies of Marx and of Siebeck have shown that the curve representing the dilution of the blood following the intake of water is the same whether 1000 cc. or only 50 cc. have been taken. Marx found that the curve of blood dilution can be obtained without the drinking of water when a susceptible person is in a hypnotic trance, simply by suggestion that the person is drinking water.¹

The function of the kidneys as part of this mechanism for water regulation is to excrete the excess of water presented to it by the blood stream. But, when the water of the organism, especially of the blood, is in danger of being diminished below the normal limit, it is also the function of the kidneys to reduce its excretion to the very minimum necessary to keep the waste substances in solution.

A third function which the kidneys exercise is in helping to maintain the normal acid-base balance in the internal milieu. For the maintenance of this balance there are other mechanisms in the body, and the kidneys add their help. When an excess of acid is present in the body they retain base by the excretion of acid phosphate. It is possible that ammonium, which the organism makes use of to neutralize acid, is formed in the kidneys themselves.

The Maximal Capacity of the Kidneys. Of these three functions, namely, the removal of the waste substances of protein metabolism, the regulation of the water content of the blood and the regulation of the acid-base balance in the body, the second one mentioned, that of water regulation, is the most sensitive function. The kidneys react very quickly to any disturbance in water regulation. Whenever water is being lost from the blood stream by other channels the excretion of water through the kidneys is diminished to an extreme degree, although the waste substances accumulate in the blood. Thus, it is this function of water excretion which can most easily be made use of to estimate what the functional abilities of the kidneys are.

The largest amount of water which the kidneys can excrete continuously is probably very difficult to estimate. Cushny puts it at 1 liter an hour. Cases of diabetes insipidus, in which 20 liters of urine have been eliminated in one day, have been reported. Cases in which 12 liters a day are excreted are more frequent. We can, therefore, say that the elimination of 1 liter of water in two hours is within the functional capacity of the normal kidneys. Although this is probably not the maximal ability of the kidneys, we may make use of it as such, and we may rightfully assume that normal kidneys are able to eliminate this amount in the time mentioned. It is a

matter of frequent observation at the present time that in normal individuals the intake of 1 liter of water is followed within two and a half to three hours by its elimination, and diuresis begins one-half to three-quarters of an hour after the intake. The functional ability of the kidneys to excrete promptly an excess of water has been made use of in the so-called water test of Volhard: 1500 cc. or, better still, 1000 cc. are taken on an empty stomach and the time of its elimination observed. We expect it to be completely eliminated in two and a half to three and a half hours. This is what we assume, in a practical way, to be the maximal limit of what the normal kidneys can do in regard to their most sensitive function in one direction.

In another direction, in preventing the elimination of water when the water content in the blood threatens to be reduced, the kidneys are equally efficient. The non-elimination of water may go on to complete suppression of urine when there is extreme loss of water through other channels, such as occurs in cholera. When this occurs the waste substances are not eliminated from the blood. Ordinarily, however, starting with the normal water content of the organism, when water is withheld for twenty-four hours, the waste substances in the blood are excreted completely, but in as little water as is necessary to keep them in solution. This is familiar to us in the concentrated urine observed normally when we sweat a good deal and do not drink sufficient water to make up for the loss, and in the concentrated urine in fever. The degree of concentration has its limits, and as we measure the concentration by the specific gravity of the urine this limit is easily ascertainable. In fact, we know that in the protein and sugar-free urine the specific gravity rarely reaches above 1030 to 1036. In practice, we take these figures on the expression of the maximal ability of the kidneys to conserve water for the organism and still excrete completely the waste substances of protein metabolism.

We have then, as the expression of the maximal capacities of the normal kidneys, the ability to excrete a given amount of water in a certain limited period; their ability to conserve water for the organism by excreting the waste substances in a definitely concentrated form.

The manner in which the kidneys perform this function is familiar to us. In the arterial system of the kidneys there is interpolated an enormous capillary surface in a very compact form—the glomeruli. As the blood passes over this capillary surface, a de-proteinized solution containing the other constituents of the blood plasma passes through these capillaries and their covering membrane of Bowman's capsule. In addition to the blood pressure, which helps to separate this solution from the proteins of the blood plasma, its passage through the glomerular membrane follows, in all probability, those laws which govern the passage of solutions through

any living membrane of many layers, laws which have recently been studied by Wertheimer in Abderhalden's laboratory, and by others. The passage of such solutions through living membranes is evidently different from filtration and diffusion through a dead membrane.

This enormous capillary surface is obviously not always open in its entirety for the passage of blood over it. For, if we assume that all the capillaries of the glomeruli are open when the kidneys are excreting $\frac{1}{2}$ liter per hour, it is evident that they cannot also all be open when the kidneys are excreting only $\frac{1}{2}$ liter in twelve hours. The fact that only a limited number of capillaries are open at one time, and that the number of open capillaries is dependent upon the amount of water which the kidneys have to excrete, has been demonstrated by Professor Richards. The ability of the kidneys to vary the number of active glomeruli, and of active capillaries in a single glomerulus, explains their ability to adapt themselves to all the changes which threaten the water content of the organism and especially of the blood.

When the protein-free solution has passed out of the arterial system, it again passes over an enormous surface—the lumen of the convoluted tubules, the cells of which abstract and absorb those substances which the organism needs in its economy, namely, water, sugar, salt and base. The longer the solution remains in contact with the cells of the tubules, the more water will be absorbed and the more concentrated is the final product. The loop of Henle acts as a pressure reservoir which serves to keep the solution in contact with the cells for a longer period. The greater the amount of the protein-free solution passing through the glomerular capillaries, the greater will be the flood coming down the tubules, the smaller will be the amount absorbed by the cells of these tubules. With a smaller amount coming down, the fluid moves with less speed, more water is abstracted and the final product is more concentrated. The ability of the kidneys to concentrate the urine to a maximum degree is, therefore, dependent (1) on the glomeruli which limit the amount of fluid passing through their capillaries, and (2) upon the maximal absorption by the cells of the convoluted tubules.

So far we have spoken of the maximal ability of the kidneys as expressed in its most sensitive function, that of helping to maintain the volume and water content of the blood within normal limits. What is the minimum which is required of the kidneys?

The Minimum Required of the Kidneys. In their function to help maintain the blood volume, the kidneys constitute one of many organs. In the excretion of the waste substances of protein metabolism the kidneys alone are concerned, for the excretion of urea through the skin is minimal and of no practical importance. We must, therefore, demand of the kidneys that they excrete under all possible conditions these waste substances, urea, uric acid, creatinin

and perhaps some undetermined substances which make up the rest of the undetermined portion of the total nonprotein nitrogen of the blood. This is the minimum which the kidneys must do. The normal kidneys have no difficulty in excreting these substances even with a maximal protein intake, and even the ingestion of large amounts of urea is quickly followed by their elimination.

When is the minimal limit reached? How much kidney substance can be lost or destroyed, and the rest of the kidneys still be able to excrete the waste substances of protein metabolism from the blood? The factor of safety varies with the individual organ, and it has been shown experimentally on animals that with the removal of almost two-thirds of kidney substance, the rest is still able to excrete all of the waste substances from the blood. When more kidney substance is destroyed the waste substances cannot be excreted and accumulate in the blood.

Renal Insufficiency. Our understanding, then, of normally and sufficiently functioning kidneys is, that the kidneys are able to excrete an excess of water in a certain minimum period of time; that they are able to concentrate the urine to a certain maximum degree; that they are able to eliminate the waste substances under all possible conditions of protein intake. The kidneys are insufficient when they are unable to do this, that is, when they are unable to concentrate the urine to a certain maximum degree; when they are unable to excrete the waste substances under all possible conditions.

The function of excreting the waste substances, being the minimal requirement for the normal functioning of the kidneys, is last to diminish. When this function is lost to a degree where, with the intake of a minimum amount of protein necessary to replace the wear and tear of the body, the waste substances are not eliminated, the kidneys are totally or completely or absolutely insufficient. The evidence and the measure of this absolute insufficiency is the amount of the waste substances, namely, the total nonprotein nitrogen, and the urea, uric acid and creatinin, in the blood.

Between the normally functioning kidneys and the absolutely insufficient kidneys indicating the destruction of at least two-thirds of functioning substance, there is a wide field. All grades of prolongation of water excretion above the minimum requirements and all grades of diminution in the ability of the kidneys to concentrate the urine occur with kidneys which are still able to excrete the waste substances of protein metabolism. We speak of such kidneys as being relatively insufficient or insufficient to a certain degree, and we use especially the maximum concentration of the urine to designate the degree of renal insufficiency. When the highest specific gravity of the urine cannot go above 1018 we know that the kidneys are insufficient to that degree, although the waste substances are completely eliminated.

Relative renal insufficiency is thus dependent upon the exclusion

of a certain number of glomeruli and of tubules from the functioning part of the kidneys. As this functioning part, the number of active glomeruli and tubules, becomes smaller and smaller, the elimination time of an excess of water becomes longer, and the ability to concentrate as measured by the specific gravity of the urine becomes less and less. When total insufficiency is reached the ability to concentrate has reached its lowest ebb. The specific gravity of the urine then remains fixed at about 1010 or 1012, and the molecular concentration of the urine is practically the same as that of the protein-free blood plasma.

Such is our present conception of renal insufficiency, relative and absolute. Aside from the chemical examination of the blood, the tests for determining renal insufficiency and its extent are very simple indeed, namely, the water and the concentration tests.

When do we find renal insufficiency? In its typical form we find it whenever there is a gradual destruction of glomeruli, and secondary to this the loss of the corresponding tubules. This is the case in chronic glomerulonephritis and in certain cases of diseases of the arteries and arterioles in the kidneys. We can follow here the gradual progress of relative insufficiency into absolute insufficiency of the kidneys. Renal insufficiency is, of course, also found in extensive destruction of the kidneys due to the so-called surgical diseases of the kidneys. We also find renal insufficiency whenever the blood plasma is prevented from reaching the filtering membrane in the glomeruli. This occurs: (1) In acute diffuse glomerulonephritis, where the glomeruli are filled with a cellular exudate which prevents the blood from passing through their capillaries in sufficient amount; (2) with a general contraction of the small arteries and arterioles in the kidneys, such as occurs in reflex anuria from a stone in the ureter, and in some cases of lead poisoning; (3) whenever water is diverted from the blood stream into other channels in large amounts, and the organism attempts to conserve its water by shutting the glomerular capillaries. This occurs in cholera, when water is lost from the body through the alimentary tract. It also occurs in high intestinal obstruction, where through the loss of water by vomiting and because of the paralysis of the splanchnic circulation, the water content of the blood threatens to become diminished. In such cases there is an increase in the waste substances in the blood, although the glomeruli are not diseased, but because the blood plasma is prevented from reaching the glomerular membrane through which the water must pass. In bichlorid of mercury poisoning there is often anuria, and with it there is, of course, renal insufficiency and the accumulation of waste substances in the blood. Here the glomeruli are not inflamed but are markedly congested, and it may be assumed that the mercury which like all heavy metals is a capillary poison has injured the glomerular capillaries to such a degree that they have lost their contractile

power. The blood passing through these capillaries passively dilates them, ruptures some of their walls, chokes most of them, so that blood circulation in the glomeruli soon ceases and glomerular filtration becomes impossible.

So much for the concept of renal insufficiency.

II. Uremia. Another concept in connection with diseases of the kidneys in uremia. Our conception of uremia has undergone considerable change in recent years, mainly as a result of the application of chemical studies of the blood and of routine blood-pressure examinations to clinical medicine. The term uremia literally means an increase of urea in the blood, and the earliest observers after Bright who found an increase of urea in the blood assumed that the clinical symptoms of uremia were due to this increase. It was found, however, that symptoms, especially of the central nervous system, occurred in Bright's disease whether urea was increased in the blood or not, and so the hunt began for some substance, the presence of which would explain the occurrence of all the various symptoms usually connected with the term uremia. Nearly all the various constituents of the blood plasma and of the urine were successively held responsible—urea, ammonium carbonate, uric acid, potassium salts, other salts, creatinin, various hypothetical organic substances, acid substances and many others. Even recently, a toxic base, which causes convulsions in guinea pigs, was held to be the causative agent of uremia.

It probably would have been better for the concept of uremia if the original assumption that the symptoms are caused by the retention of urea in the blood would have been adhered to. One of the reasons for rejection had been that many investigators had injected urea into the blood stream of animals and had found that it was quickly excreted without producing any symptoms. It seems laughable to us when we read that conclusions were drawn from the injection of 3 or 4 gm., even when injected after the extirpation of one kidney. At the present time 30 to 50 gm. of urea and even more are given by some clinicians in the treatment of edema without producing any symptoms and with the prompt elimination of the injected urea. Hence it is even now generally assumed that urea cannot be the substance causing uremic poisoning, since the ingestion even of large quantities does not cause any harm. This is true in persons with normal kidneys, but is it also true of the concentrations of urea found in the blood in the terminal stage of nephritis?

The Occurrence of Convulsions in Nephritis. The question, therefore, which arises in the observation of cases of Bright's disease is: Why do certain symptoms, coma and convulsions, occur in some cases of Bright's disease, whether the waste substances in the blood are increased or not, and why do they not occur in others in which the waste substances are also increased? In cases of anuria from obstruction of both ureters, in which all the urinary substances are

retained in the body, convulsions are uncommon and are not part of the clinical picture, and for many days the patient may not show any symptoms of poisoning.

Here the chemical studies of the blood, blood-pressure determinations and the observation of the retinal arteries in cases of nephritis have come to our help. We have definitely learned that convulsions do not belong to the clinical picture of poisoning by the waste substances, as in complete anuria. We have also learned that convulsions in nephritis are always preceded by a sudden rise in blood pressure; that accompanying the increase in blood pressure there is an arterial contraction which may be general, but which certainly occurs in the brain; that, as evidence for the occurrence of the arterial contraction in the brain we have the narrowed arteries in the retina which we can observe directly. We have learned that such a sudden increase in blood pressure, which is followed by tonic and clonic convulsions, or equivalent phenomena, such as sudden blindness and various forms of temporary paralysis or paresis, occur especially in the course of acute diffuse glomerulonephritis, or in the course of chronic hypertension, whether there is an increase in the waste substances of the blood or not. Ascoli, Strauss, and especially Volhard, have taught us to separate these convulsive seizures from true uremia. Even the name convulsive uremia should be abandoned and it is much better to speak simply of convulsions occurring in the course of acute or chronic nephritis.

True Uremia. With the separation of the convulsive phenomena from the clinical concept of uremia, there remain the symptoms which we connect with the retention of the waste substances in the blood, true uremia. We best gain an understanding of uremia when we follow the progress of absolute renal insufficiency in the course of chronic nephritis.

What strikes our notice at first in following a case of slowly progressive renal insufficiency is the pallor of the patient, as the basis for which there is a real moderately severe anemia. There is nothing specific in this anemia, but it commonly precedes the other symptoms and is of diagnostic value in calling attention to the possible presence of renal insufficiency. The anemia probably expresses a diminution in the regenerative powers of the hemopoietic apparatus.

As the waste substances in the blood increase in amount, the urea nitrogen which ordinarily forms about half of the total non-protein nitrogen, now constitutes about 70 per cent. When the total nonprotein nitrogen in the blood reaches to about 100 mg. per 100 cc., all the tissues of the body contain a large amount of urea. The other waste substances in the blood, namely, uric acid and creatinin, are present in comparatively small amounts as compared to urea, and we can, therefore, neglect them as factors in the causation of uremic symptoms. The urea which diffuses easily

everywhere is present in every organ in excessive amounts. We now begin to notice symptoms due to the excretion of urea into the gastrointestinal tract. The presence of urea in the salivary glands leads to its excretion into the mouth, to its decomposition with the formation there of ammonium and to the odor of urine from the mouth. This leads to the presence of a disagreeable taste in the mouth, a coated tongue and anorexia. The presence of urea in the glands of the stomach leads to its excretion there, to the irritation of the mucous membrane of the stomach and to nausea and vomiting. The presence of urea in the glands of the intestinal tract leads to its excretion there, to the irritation of the intestinal mucous membrane, to diarrhea and to the formation of ulcers in the intestinal tract.

Increased excretion of urea through the skin also occurs, and itching is a frequent symptom, as is also an occasional dermatitis.

The gastrointestinal symptoms are frequently the only ones for a long period. As the urea nitrogen in the blood increases still more, all the organs in the body are practically saturated with urea. We now begin to notice the essential phenomena of true uremia, the symptoms due to retention of the waste substances in the tissues and organs, namely: (1) A gradually increasing narcosis, fatigue, drowsiness, stupor and eventually coma; (2) an increased irritability of the muscles, characterized by twitching of the muscles, tendon jumping and choreiform movements; (3) the gradual development of slow and deep breathing. Convulsions are not part of this picture, although convulsions do occasionally occur before death.

The slow and deep breathing is a phenomenon familiar to us. We recognize it as the breathing which we find in diabetic acidosis, and it is known by the name of its discoverer, Kussmaul. When we now examine the blood for its carbon dioxid content we find this to be reduced. There is a loss of alkali reserve. We know then that the third function of the kidneys, that of helping to maintain the acid-base balance in the body, has been lost. The kidneys are unable to excrete the fixed acids, and the retained acid phosphate deprives the bicarbonate of its base.

For the other two sets of symptoms, the mixture of narcosis and of muscular irritability, there is no definite and accepted explanation. Investigators are still looking for some mysterious poison. It seems to me that both of these sets of symptoms can be explained by the presence in the tissues of the enormous amount of urea. We must remember that, although urea is a harmless substance when it can be excreted within a short time, its continued presence in the tissues in such concentration as found in chronic uremia is an entirely different thing, and probably not at all harmless. Urea is known to have a narcotic effect on the central nervous system and derivatives of urea are made use of to produce narcosis in animals. In an experiment with some other object in mind, Gabbe found that

the presence of an increased amount of urea in a muscle caused an increased irritability of the muscle.

Experimentally, the problem has been attacked by the injection of urea into the blood stream of animals. Large quantities are necessary if the concentration in the blood is to remain high, and with normal kidneys it can only remain so for a short period. Among others, Leiter found that symptoms similar to uremia, although more violent, were produced by the injection of large amounts of urea in the blood. These experiments are, of course, not sufficient to settle this question. I think the point of attack must be a little different. In the experiment the kidney tissue should be removed to the extent where retention of the waste substances in the blood is just avoided. This should then be followed by the injection of urea into the blood stream and its concentration there should be maintained for a long time at a level corresponding to the figures found in uremia in man. Such experiments may eventually solve this problem.

In our present understanding of uremia there are thus involved two distinct concepts: One, which explains the appearance of convulsions and equivalent phenomena as the result of sudden arterial contraction in the brain, and occurring as an incident in the course of nephritis; the other, which explains the phenomena of true uremia as a result of the retention of the waste substances, chief of which is urea, in the blood. It is my own firm conviction that the phenomena of brain narcosis and increased muscular irritability are the result of poisoning by the large amounts of urea remaining for long periods of time in the respective organs.

III. Nephrosis and Lipoid Nephrosis. Another concept current at the present time is that of nephrosis, especially lipoid nephrosis. The term nephrosis is an unfortunate one, because it stands for two concepts, a pathological and a clinical. The term was first introduced by Müller, in 1905, to designate tubular degeneration in contradistinction to nephritis or glomerular inflammation. At that time it was not possible to separate clinically these two classes of kidney diseases. The term nephrosis does not appear again in the literature until Volhard and Fahr made use of it in their monograph in 1914. From then on it is current both clinically and pathologically.

Volhard, who is a master mind in this field, clearly recognized the connection between glomerular inflammation and the accompanying clinical phenomena of hematuria, increase in blood pressure and renal insufficiency. It was, therefore, necessary for him to separate those cases in which inflammation of the glomeruli is not found, but which present clinical evidence of renal disease, such as albuminuria and edema. Volhard used the term nephrosis for this group of cases. It was a very mixed group, and the pathologic changes found in the kidneys included all the forms of tubular degeneration, albuminoid, hyalin, fatty, lipoid and amyloid degen-

eration and necrosis of the tubules such as is found in bichlorid of mercury poisoning, all without any histologic evidence of inflammation in the glomeruli. Fahr, the pathologist, used the term nephrosis to include all these forms of degeneration and also necrosis.

It is obvious that as a pathologic concept the term nephrosis is not as good as the term tubular degeneration. Also, necrosis is really not degeneration, so that both Fahr and Volhard spoke of specially characterized nephrosis, necrotizing nephrosis. The term nephrosis, however, has come to stay and when used in the pathologic sense as including various forms of degeneration or necrosis which are found histologically, we have no fault to find with it. It is quite another thing when we attempt to correlate all these forms of degeneration with clinical pictures. In febrile diseases we often find clinically a mild albuminuria and cloudy swelling of the cells of the tubules histologically. To speak, therefore, of the nephrosis of typhoid fever or of pneumonia, is to raise an unimportant clinical symptom to the dignity of a disease. In addition, we must not forget that albuminuria is a glomerular symptom. The proteins of the blood pass into the urine through the glomeruli and not through the tubules. In amyloid disease we have amyloid deposits in the glomeruli also. Fatty degeneration of the cells of the tubules in Graves' disease does not cause any renal symptoms; similarly glycogen deposits in the cells of the tubules do not cause any symptoms. In bichlorid of mercury poisoning there is necrosis of the cells of the tubules, and there is only congestion in the glomeruli. Here, however, hematuria occurs as well as anuria, both of which are glomerular symptoms, and sometimes with the anuria there is an increase in blood pressure.

We must, therefore, be very careful in attempting to correlate tubular degeneration with clinical phenomena. We may, however, use the term nephrosis in a clinical sense, and include under this term, not all possible forms of tubular degeneration in the manner of the pathologist, but a certain small well-defined group of kidney diseases. This group includes the bichlorid of mercury kidney, amyloid disease of the kidneys, possibly also the kidney of pregnancy, and the disease now called lipoid nephrosis. These four diseases of the kidneys have distinct clinical pictures, in the case of amyloid disease perhaps not so distinct, and they have this in common, that the glomeruli do not show any inflammatory changes. My own opinion is that it is much better to characterize each disease especially as I have done, and speak of the bichlorid kidney, the amyloid kidney and the kidney of pregnancy instead of speaking of them as nephrosis.

Lipoid Nephrosis. This brings us to lipoid nephrosis. It was particularly this disease which lead Volhard to revive the term nephrosis. Among his material there was a group of cases which presented a distinct and definite clinical picture—oliguria with

marked albuminuria; marked edema with hydrothorax and ascites; increase of lipoids in the blood; absence of hematuria, of hypertension and cardiac hypertrophy and of renal insufficiency. The cases began insidiously, ran a chronic course and most of them terminated fatally with pneumococcus peritonitis. On examination, the glomeruli were found to be normal and lipid deposits were found in the cells of the tubules and in the interstitial tissue of the kidneys.

The necessity of separating these cases from similar ones with hematuria, hypertension and renal insufficiency, led Vollhard to classify them as cases of nephrosis. Because of the absence of a definite etiology, and because of the distinctive clinical picture, he spoke of them as "genuine" nephrosis, also as chronic cases of nephrosis. Munk, who had seen similar cases, found lipid granules in the urine, and lues as an etiologic factor. In this country Epstein, who had seen similar cases, found a reduction in the proteins of the blood. The reduction is in the albumin fraction of the proteins, the globulin remaining normal or becoming increased. He also found an increase in the cholesterol of the blood. These observations were corroborated by others. Because of the presence of lipoids in the urine and in the kidneys, and because of the increase amount of cholesterol in the blood, Munk used the term lipid nephrosis to characterize this disease. Others, including Fahr, have accepted this term. This term simply denotes a certain symptom complex and has no connotation indicative of pathogenesis or etiology. The presence everywhere of lipoids is, in all probability, a secondary characteristic in the course of the development of the disease.

We have thus among our concepts of kidney diseases two which are designated by the term nephrosis: (1) A pathologic concept, which includes all forms of degeneration, but which adds nothing to our understanding of kidney pathology; (2) a clinical concept which includes certain definite clinical entities, which are characterized best, however, by other terms, with the exception of one form which we have called lipid nephrosis, and which presents a definite symptom complex.

I say symptom complex advisedly. For it frequently happens that we have under observation a case of renal disease, presenting all the symptoms of lipid nephrosis, namely, marked albuminuria, oliguria, marked edema, lipoids in the urine, increase of cholesterol in the blood, diminution of albumin in the blood and the absence of hypertension and renal insufficiency, only to find after one or two years or even sooner, that hypertension and renal insufficiency supervene. Here we have the symptom complex of lipid nephrosis as a transitory phase in the course of chronic glomerulonephritis. In fact, this symptom complex is much more frequently found in the course of subchronic and chronic nephritis than as a disease by itself. Pure lipid nephrosis is a rare disease. Fahr was only able

to examine the kidneys of 9 cases up to 1922. The disease does occur, however, and seems to be more common in children.

When we meet this symptom complex of lipid nephrosis without evidence of chronic nephritis, we are, of course, unable to tell whether we are dealing with pure lipid nephrosis or with this symptom complex occurring as a transitory phase in the course of chronic nephritis. Only the eventual course of the disease can determine definitely the diagnosis. For the last four years I have been having under observation a patient, presumably with lipid nephrosis, who has at various periods taken as much as 3 to 4 gm. of thyroid extract for the treatment of his edema. I am still not sure whether I am dealing with a case of pure lipid nephrosis or whether the symptoms of chronic nephritis will not eventually appear.

The Pathogenesis of Lipid Nephrosis. I think that the pathogenesis of a symptom complex such as that of lipid nephrosis, occurring sometimes in pure form, and at other times in combination with nephritis, is probably the same in each case. Occasionally one has the opportunity to observe a case of acute diffuse glomerulonephritis which subsides and is followed months later by the development of all the phenomena of lipid nephrosis. This has been my experience as well as that of others. It seems to me that as a result of the acute diffuse nephritis, the glomerular membranes consisting of the capillary walls and the covering layer of Bowman's capsule have lost their function of holding back the proteins of the blood from passing through them, even though the exudate in the glomeruli has been absorbed, and the acute nephritis apparently healed. As a result of this loss of function, there remains a marked albuminuria in such cases, and the loss of albumin from the blood becomes so large that the reduction in the blood is noticeable. The organism attempts to replace the albumin lost from the blood plasma by the production of globulin which has a larger molecular aggregate and is more easily held back by the glomerular membranes. When the organism is able to do this the globulin in the blood plasma is increased, and, in fact, a slight increase in globulin is characteristic of this disease. Salvesen reported an interesting case, in which the loss of large amounts of albumin in the urine was accompanied by an increase in the proteins of the blood to as high as 10 per cent, of which the greater part was globulin.

When the organism is unable to compensate the loss of albumin by a corresponding increase in globulin the proteins of the blood remain at a low level. The inability on the part of the organism to regenerate the lost protein seems to be the result of a general depression of many vegetative functions, including the oxidative functions of the cells. This finds expression in the lowered basic metabolic rate and in the lowered resistance to infection. The increase of cholesterol in the blood is probably a secondary phenomenon due to a disturbance of nutrition in the cells, such as occurs also in diabetes.

When the organism is thus unable to replace the lost protein by the production of new, it attempts to limit the loss through the kidneys by limiting the amount of urine. A diminution in urine is characteristic of lipid nephrosis. With a normal water intake and the diminution in the amount of urine, there is soon an increase in the water content of the body. With the water content of the blood remaining normal, the excess must accumulate in the tissues and hence the edema.

We can thus explain the various manifestations of the symptom complex of lipid nephrosis, as the consequence of the continued loss of albumin, as the result of the inability on the part of the organism to replace the lost albumin, and as a result of the depression of certain vegetative functions. The loss of albumin must necessarily be due to some defect in the glomerular membrane through which the albumin passes. This defect can be ascribed to a previous acute nephritis which has healed but has left the glomerular membrane permanently defective, even when no such defect can be found histologically. The result is a case of pure lipid nephrosis. The toxin of lues may possibly have a similar effect on the glomerular membrane.

An acute diffuse nephritis which does not heal completely, but passes gradually into the subchronic or chronic forms, may have the same effect in damaging the glomerular membrane. The consequence is a continuous marked albuminuria, and, secondarily, the development of the symptom complex of lipid nephrosis. In this case, however, this symptom complex occurs in the course of subchronic or chronic glomerulonephritis.

IV. Benign and Malignant Renal Sclerosis. Another concept in modern use is that of renal arteriosclerosis without renal insufficiency and with renal insufficiency, or benign and malignant renal sclerosis. This concept is also of recent development, and to understand it we must know how the groups of cases included under the term of arteriosclerosis came to be separated from other groups of Bright's disease or nephritis. The pathologic anatomy of nephritis has its foundation in the work of Loehlein. In 1907 Loehlein published a study of 30 cases of nephritis in which the importance of the glomeruli in the pathology of nephritis was definitely established. Loehlein showed that all the forms of nephritis which we now call glomerulonephritis have their beginning in an acute diffuse inflammation of the glomeruli. He showed further that all cases of glomerulonephritis which are of longer duration than the acute form fall in three groups. The cases of the first group have a short and stormy course. These cases correspond to our conception of subacute diffuse glomerulonephritis, and end fatally within a few months. In the cases of the second group the character of the disease is milder and the duration is longer. These cases correspond to the subchronic form and last longer than a few

months, even as long as one or two years. The cases of the third group run a very chronic course from a few years to as much as twenty-five years.

These groups, the acute, the subacute, the subchronic and chronic forms of diffuse glomerulonephritis, together with the relatively benign focal glomerulonephritis, constitute by far the greatest number of cases included under the term nephritis. All these cases present inflammatory changes in the glomeruli, exudative and proliferative in the acute and subacute forms, with the addition of hyalinization and obliteration of the glomeruli in the chronic forms.

The recognition and separation of these groups of cases pathologically was accomplished by Loehlein and corroborated by others. Their clinical separation and their recognition as clinical entities was especially aided by Volhard.

Renal Arteriosclerosis. With the separation of these groups of cases there remained one group, the cases of which also showed obliteration of the glomeruli. Some of the cases of this group were accompanied by total renal insufficiency, while others were not. In addition to the obliteration of the glomeruli there was also found marked arteriosclerosis of the small arteries and arterioles. The importance of the renal vessels in the pathology of Bright's disease had been recognized long ago by Gull and Sutton. They found a hyalin-fibroid substance in the muscularis of the small arteries and in the walls of the capillaries, and characterized the disease as a generalized arteriocapillary fibrosis. The arterial changes in the kidneys were further studied by Ziegler, who showed the importance of arteriosclerosis in kidney disease. But it was only with the recognition and separation of the diseases of the kidneys due to the inflammation of the glomeruli, that the importance of the arterial changes for the remaining group of cases was recognized. The pathology of arteriosclerosis of the kidneys was studied by a group of pathologists, among whom the names of Jores, Loehlein, Aschoff, Fahr and Herxheimer stand out preëminently.

It was established that in certain kidneys in which the glomeruli are not inflamed, there is found a hypertrophy and thickening of the walls of the small arteries and arterioles, hyalin and fatty degeneration of the thickened intima and narrowing of the lumen of these vessels. It was also found that as a result of extreme narrowing and complete occlusion of the small arteries, such as the interlobular arteries and the afferent arteries of the glomeruli, the corresponding glomeruli do not receive blood, become collapsed, then surrounded by connective tissue and finally completely obliterated. The cause of the obliteration of the glomeruli is evidently to be found in the occlusion of the small arteries and the arterioles. Individual investigators applied different names to these forms of kidney diseases, and we read of nephrosclerosis, nephrocirrhosis arteriosclerotica, arteriosclerosis of the kidneys and renal arteriolo-

sclerosis. All these names meant to convey that there is a reduction of kidney volume as a result of arterial change. The important element, however, is the arterial change and not the reduction in kidney substance. The term renal arteriosclerosis conveys this meaning and it has become one of our concepts in diseases of the kidney.

So far the concept of renal arteriosclerosis had only a pathological meaning. It remained for a clinician—Volhard—working in conjunction with a pathologist—Fahr—to give the concept a clinical meaning. Volhard demonstrated that certain cases in which the kidneys show arteriosclerosis with obliteration of some of the glomeruli, without any inflammatory changes in them, and with a greater number of glomeruli not at all affected, run a clinical course with the prominent symptom of chronic hypertension without the presence of renal insufficiency. These cases of chronic hypertension, of which we see so many and which are familiar to all of us, have been known to us under various names, such as benign hypertension, essential hypertension, the presclerosis of Huchard, the hyperpiesis of Allbutt. The hypertension becomes permanent in late middle life, not in senium but in senescence, as Allbutt says. These patients carry their high blood pressure for many years. They do not die of renal insufficiency, but of intercurrent infections, or of diseased coronary arteries of the heart, or of arterial disease of the brain. The absence of renal insufficiency speaks for the slow progress of the arteriosclerosis in the kidneys and Loehlein spoke of these cases as *nephrocirrhosis arteriosclerotica lenta*.

We have then corresponding to the concept of renal arteriosclerosis without renal insufficiency, or benign renal sclerosis, a disease, characterized clinically by chronic hypertension without renal insufficiency, and characterized anatomically by arteriosclerosis of the small arteries and arterioles in the kidneys with narrowing of their lumen, and obliteration of some of the glomeruli, without any inflammatory changes in them, and leaving a sufficient number of glomeruli intact to perform the function of the kidneys.

Malignant Renal Sclerosis. With the separation of this large group of chronic hypertension without renal insufficiency, there remains a small group of cases in which after prolonged hypertension renal insufficiency supervenes. These cases correspond to the primary contracted kidney or the genuine contracted kidney of the older clinicians. Their separation from chronic glomerulonephritis was accomplished by Volhard and Fahr. Volhard found that among the cases of chronic hypertension in which renal arteriosclerosis could be assumed to be present, there were some in which the hypertension was of an extreme degree and in which total renal insufficiency gradually supervened in the same manner as in chronic glomerulonephritis. When Volhard and Fahr examined the kidneys of these cases they found the arteriosclerosis of the small arteries

and the arterioles to be of an extreme degree. The arteries and the arterioles were thickened, with fatty and hyalin degeneration of their walls, in many the lumen was completely closed and very many glomeruli were completely obliterated. The changes found in chronic glomerulonephritis were not found in these cases. Evidently these cases presented an advanced degree of renal arteriosclerosis. But Volhard and Fahr found more. The arteries and the arterioles in the kidneys showed an inflammation of the intima and necrosis of the vessel wall in an irregular distribution, an arteriolitis and an arteriolonecrosis. In addition, the glomeruli showed small areas of inflammation in an irregular focal distribution. Evidently a focal inflammatory process of the arterioles and glomeruli had been added to the arteriosclerosis. Volhard and Fahr, therefore, spoke of this form of kidney disease as the combination form. Both, however, dropped this term later. Volhard speaks of this form as the ischemic end stage of arteriosclerosis, while Fahr calls it malignant renal sclerosis. I have preferred the term renal arteriosclerosis with renal insufficiency, but the term malignant renal sclerosis really expresses the same thing and is much shorter.

These cases of malignant renal sclerosis or renal arteriosclerosis with renal insufficiency increase in frequency with the closer acquaintance with this form of kidney disease. Klemperer reported a study of 18 cases at a meeting of the New York Pathologic Society. Fahr assumes that the inflammatory reaction in the vessels and glomeruli is caused by a specific poison, either lead, or syphilis. In his own cases, however, there were many who did not have lead or syphilis as etiologic factors. Loehlein and Herxheimer consider the inflammatory changes as reparative, due to the collapse of some of the glomeruli. Loehlein considers the whole process as an extreme degree of renal arteriosclerosis and calls this form of kidney disease *nephrocirrhosis arteriosclerotica progressa*. Cases of renal arteriosclerosis with renal insufficiency, in which the inflammatory changes are absent, also occur.

We have then corresponding to the concept of renal arteriosclerosis with renal insufficiency, or of malignant renal sclerosis a disease which is characterized clinically by hypertension of many years, to which renal insufficiency is gradually added. It is characterized pathologically by an extreme degree of arteriosclerosis, with the addition in the greater number of cases, of an arteriolitis and an arteriolonecrosis in a focal distribution.

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STUDIES OF SERUM ELECTROLYTES. VI. WATER METABOLISM IN PNEUMONIA.*

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In previous papers^{1,2,3} the authors presented data on the distribution of electrolytes in the body during lobar pneumonia. The possibility that the decreased concentration of the total base, chlorid and protein of the serum during the active infection might be due in part to a retention of water in the body and a dilution of the serum has been discussed. The present paper is concerned with our observations of the water metabolism in patients suffering with lobar pneumonia and with a consideration of the factors involved in the calculation of the water balance.

From the beginning, the difference between changes in the water balance and changes in the percentile water content of tissue should be kept clearly in mind. The water balance represents the difference between the total water intake and the total water output, and while this quantity includes the water of oxidation of the foods it does not take into account the water exchange of the tissues when they are metabolized. As it is generally recognized and as the data in this study demonstrate, the diet during the precritical period of pneumonia is inadequate for the metabolic needs of the subject so that it becomes necessary for him to catabolize his own tissues. Associated with the catabolism of tissues there is every reason from studies in inanition, such as those of Benedict and his associates,^{4,5} to expect a release of preformed water from the catabolized tissues as well as the formation of water of oxidation from these tissues. If the percentile water content of the remaining tissues be unchanged, then the water derived from the catabolized tissues must be excreted and the water balance will become negative by that amount. It is thus possible to have a negative water balance without change in the percentile water content of the body tissues and likewise, if only part of the water derived from catabolized tissues be excreted, it is also possible to have a negative water balance with an increase in the percentile water content of the remaining tissues.

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In our studies we have estimated the water balance from data on intake, output and change in weight. For the interpretation of the water balance, however, we have attempted to estimate within limits the water derived from metabolized tissues.

The interpretation of the water metabolism in pneumonia and fever in general has led some to the view that there is water retention in the body and others that there is an actual diminution in the water content of the body. Much of the confusion, especially in the early literature, can be attributed to the various interpretations as to what measures the water metabolism. The workers who demonstrated by means of intake and output records that there was less water in the body during the course of a fever than at its beginning, concerned themselves with changes in what we might regard as the water balance. On the other hand, the investigators who studied such relationships as the ratio of water content to solid content in the blood, tissues, or entire body have been concerned with changes in the percentile water content of the tissues. We shall not attempt to cover the large literature on water metabolism during fever but shall merely point out some of the studies bearing on the water relations of the body during lobar pneumonia.

Leyden,⁶ in 1869, first studied the problem of water metabolism in pneumonia. He showed by means of weight studies that there was an increased loss of weight through the skin and lungs during the febrile period. At the time of crisis he observed free sweating and rapid loss of weight. The loss of weight continued even after the crisis when his patients were returning to their normal state, which he attributed to an earlier incomplete excretion of water during the febrile period.

Sandelowsky⁷ studied the serum proteins, salt balance, and body weights in 11 cases of pneumonia. He considered the serum protein an index of blood concentration. In 7 cases the body weight either increased slightly during the fever or remained constant, whereas after the crisis the weight fell more or less rapidly. During the febrile period there was generally a decreased concentration of protein, the correlation of which with the increased or constant weight Sandelowsky believed could not be explained otherwise than by an actual retention of water in the serum. In his remaining group of 4 cases there was a continued decrease in weight during the febrile and afebrile periods which Sandelowsky attributed to a loss of body tissues which overcompensated, so far as weight was concerned, for a percentile increase of water in the remaining tissues. According to him, previously healthy individuals who developed a mild pneumonia would have retention of water with increased weight, whereas, severe pneumonia cases in which there was much tissue wasting were apt to have water retention in the remaining tissues with decreased weight.

Schwenkenbecker and Inagaki⁸ studied the ratio of water to dry

substance in muscle and pieces of liver obtained from patients who died of acute febrile infections including pneumonia. They found an increase in percentile water content as a result of an absolute diminution of solids. These authors stressed the absence of water retention in the body in acute infections except when heart or kidneys were diseased.

Hutchison⁹ found a slight increase in the water content of voluntary muscle in pneumonia and Garratt¹⁰ demonstrated a small increase in the water content of heart muscle. Additional corroborative evidence dealing with increase in percentile water content of tissues should include the observations of Mayer and Schwartz¹¹ using the Schade elastometer with which they demonstrated moderate degrees of edema in subcutaneous tissues of all of their pneumonia cases; and the recent observations of Soule, Buckman and Darrow¹² on blood volume in fever in which they found that there was an increase in the plasma volume in fever accompanied by an increase in the water held diffusely throughout the body.

Materials and Methods. Our studies were carried out on 7 patients suffering with pneumonia, to 3 of whom large quantities of sodium chlorid were administered. We also report the water balance of two normal subjects who for another purpose were put for forty-eight hours upon the same limited diet which the pneumonia patients received and who during this period were sweated vigorously by light baths.

All of the subjects studied were weighed at seven o'clock each morning to within ± 10 gm. The dry weights of the ingesta and egesta were determined with the exception of the sputum and the blood removed for analysis. The sputum was arbitrarily regarded as containing 5 per cent solids. The blood solids were taken as 20 per cent of the total amount of blood removed, using Gram's average figures.¹³ For the details of our methods, the reader is referred to Paper IV of this series.²

Calculations and Results. Our method of estimating water balance from our data is indicated in the following equations. Throughout this paper an arbitrary *allowance for maximum error* has been made for each measurement and estimate. The allowance for error is designated in text and tables by the symbol \pm and must not be confused with probable error or other statistical function. No conclusions have been drawn from positive or negative balances except where they exceed the allowance for error as computed.

Calculation of Absolute Water Balance. Measured intake (grams):

$$(1) \quad I = \text{food} + \text{beverage} + \text{enema in grams} \pm 2 \text{ per cent.}$$

Measured intake of water (grams):

$$(2) \quad W_i = [\text{water of food estimated from tables (but not the water of oxidation)} + \text{beverage} + \text{enema}] \pm 2 \text{ per cent}$$

Water of oxidation of food intake (grams):

$$(3) \quad W_{ox.i} = (0.413 P_i + 0.555 C_i + 1.071 F_i) \pm 2 \text{ per cent}$$

where P_i , C_i and F_i are the grams of protein, carbohydrate and fat in the intake. The amount of water formed by oxidation is taken from Magnus-Levy's¹⁴ calculations that 100 grams of protein give 41.3 grams of water; 100 grams of carbohydrate give 55.5 grams of water; 100 grams of fat give 107.1 grams of water.

Total water intake (grams):

$$(4) \quad W_{ti} = W_i + W_{ox.i}$$

Measured output (grams):

$$(5) \quad O = (\text{urine} + \text{feces} + \text{sputum} + \text{blood removed}) \pm 2 \text{ per cent}$$

Measured water output (grams):

$$(6) \quad W_o = (W_u + W_{fec} + W_{sp} + W_{bl}) \pm 2 \text{ per cent}$$

Daily change in weight (grams):

$$(7) \quad \Delta W_t = (\text{initial weight} - \text{final weight}) \pm 20 \text{ grams}$$

Weight loss through skin and lungs (grams):

$$(8) \quad -\Delta W_{ts.l.} = -\Delta W_t - (O - I)$$

Weight loss due to excess of CO_2 in grams over O_2 in grams:

$$(9) \quad (\text{CO}_2 - \text{O}_2) = \frac{\text{Cal}_t}{\text{Cal}_{L.\text{O}_2}} \left(\frac{44.0 \text{ R.Q.}}{22.4} - \frac{32}{22.4} \right)$$

where

Cal_t = total metabolism in calories

$\text{Cal}_{L.\text{O}_2}$ = calories per liter of oxygen consumed

R.Q. = respiratory quotient

None of the quantities (Eq. 9) has been measured in our studies but they may be estimated subject to an allowance for error. Our method has been to estimate the basal metabolism for age and weight from Sage normal standards (Aub and Du Bois¹⁵) and Meeh's formula, with an addition for fever estimated by the average percentile increase of metabolism per degree increase of temperature from Du Bois' data and an additional 10 per cent during the pre-critical period for excessive protein destruction.¹⁶ The caloric range we use is from 90 per cent of this value to 1000 calories above this value and doubtless includes the true value. The range taken is given in table. The R.Q. is estimated¹⁷ by assuming complete metabolism of the food intake, a total protein metabolism measured by the urinary nitrogen, and the residual calories assumed furnished from body fat. In the table we give the values used for $(\text{CO}_2 - \text{O}_2)$

with the allowance for error. When the range of values by the above method of computation is less than ± 20 grams we have arbitrarily taken the allowance for error as of this magnitude.

Water loss through skin and lungs, neglecting the solids of the sweat which are assumed to be less than 0.5 per cent of the water loss (grams):

$$(10) \quad W_{s.l.} = [-\Delta W_{t.s.l.} - (CO_2 - O_2)] \pm \text{error. (See table.)}$$

Total water output (grams):

$$(11) \quad W_{t.o.} = (W_o + W_{s.l.}) \pm \text{error. (See table.)}$$

Daily water balance:

$$(12) \quad W \text{ Bal} = (W_{t.i.} - W_{t.o.}) \pm \text{error. (See table.)}$$

The data required for these equations is to be found in part in table and in part in Papers IV and V of this series.

The day on which the crisis occurred is designated as the O day; the days before the crisis as $-$ days; and the days after the crisis as $+$ days.

Our cases may be divided into two groups, the first group (B1, B2, B4 and B5) representing pneumonia patients under the ordinary régime; and the second group (B3, B6 and B7) representing patients receiving unusual treatment. Case B3 was given a high-caloric diet on the first two days of study (-3 and -2 days); and Cases B6 and B7 were given extra salt with their diets during the precritical period.

In the first group of our cases up to the day of crisis the water balance was between -470 and $+700$ grams including the allowance for error. During the precritical period there was a positive water balance for one day in B2 and B4 respectively. At the time of crisis each of the cases in the group showed a tendency toward increase of the negative water balance. For the most part during the epicritical period the water balance was negative except in B5 where it became positive associated with the development of a large empyema. Thus the water balance in pneumonia patients under the ordinary régime before and after the crisis was predominantly negative, although exceptions occurred in both periods.

In the second group of our cases the water balance was positive during the first day of study in B3, it was questionably positive during the precritical period in B6, and was definitely positive during the precritical period in B7. The tendency toward water retention was very prominent in B7 who had great gain in weight and eventually visible edema. B6 showed the same tendency although it was less marked. After the crisis at a time when the salt intake was decreased, the water balance became negative. Thus the water balance tended to become positive before the crisis in our pneumonia patients who received extra quantities of salt precritically, whereas, after the crisis, when the salt intake was decreased, it became negative.

DATA ENTERING INTO WATER BALANCE.

Case No.	Day from crisis.	Calorie intake.	Estimated calorie requirement, Cal.	Measured water intake, W _i .	Water of oxidation of food, W _{oxi}	Total water intake, W _{ti} .	Weight loss, skin-lungs, -ΔW _{ts} .	(CO ₂ - O ₂).	Total water output, W _{to} .	Water balance, WBal.	Estimate of water from body tissues, W _{tis} .	Direction of	
												Water balance, WBal.	Relative water balance, WBal _{rel} .
B1	-1	755	2000-3230	3999	94	4093	3040	46 ± 20	4382 ± 68	- 289 ± 150	509 ± 77	-	?
	0	799	1850-3060	3460	99	3559	2744	64 ± 20	3892 ± 64	- 333 ± 135	539 ± 75	-	?
	+1	786	1440-2595	2537	97	2634	2714	60 ± 20	3953 ± 66	- 1319 ± 119	510 ± 73	-	-
B2	-3	1067	2140-3380	3627	126	3753	2196	71 ± 20	3537 ± 68	+ 216 ± 144	587 ± 78	+	+
B3	-3	2733	3240-4600	3928	320	4248	2436	117 ± 21	3932 ± 73	+ 316 ± 158	412 ± 85	+	+
	-2	1412	3240-4600	5090	163	5253	2174	52 ± 20	5759 ± 113	- 506 ± 218	737 ± 85	-	?
	-1	33	2920-4250	3546	4	3550	2197	20 ± 20	4702 ± 91	- 1152 ± 162	1010 ± 83	-	?
	0	391	3160-4510	4523	49	4572	4276	20 ± 40	5624 ± 67	- 1052 ± 158	886 ± 85	-	?
	+1	1160	2510-3800	3763	145	3908	2584	83 ± 20	4411 ± 78	- 503 ± 156	887 ± 80	-	+
	+2	1227	2510-3800	3422	150	3572	2080	68 ± 20	4108 ± 82	- 536 ± 154	654 ± 80	-	?
	+3	1117	2510-3800	5115	136	5251	2382	57 ± 20	6409 ± 122	- 1158 ± 227	750 ± 80	-	-
	+4	1500	2050-3280	3904	184	4088	2274	80 ± 20	5117 ± 99	- 1029 ± 181	485 ± 77	-	-
	+5	1002	2050-3280	3441	126	3567	1829	80 ± 20	4061 ± 86	- 494 ± 158	597 ± 77	-	?
	+6	1060	2050-3280	2775	134	2909	1997	80 ± 20	4354 ± 89	- 1445 ± 148	509 ± 77	-	-
	+7	555	2050-3280	2906	70	2976	1690	58 ± 20	3551 ± 78	- 575 ± 137	599 ± 77	-	?
B4	-2	800	2410-3680	4525	101	4626	3223	63 ± 20	4619 ± 69	+ 7 ± 162	838 ± 79	?	+
	-1	939	2340-3600	6035	117	6152	3223	77 ± 20	5663 ± 90	+ 489 ± 213	825 ± 79	+	+
	0	861	2210-3480	4022	107	4129	3086	62 ± 20	6067 ± 101	- 1938 ± 184	820 ± 78	-	-
	+1	798	2210-3480	3202	99	3301	2554	50 ± 20	5118 ± 106	- 1817 ± 172	706 ± 77	-	-
	+2	698	2040-3270	2183	88	2271	1909	58 ± 20	3301 ± 69	- 1030 ± 115	667 ± 77	-	-
	+3	936	1800-3000	4346	116	4462	1689	63 ± 20	4239 ± 92	+ 223 ± 181	571 ± 75	+	+
	+4	1014	1630-2810	3425	127	3552	1631	75 ± 20	4590 ± 101	- 1038 ± 173	395 ± 74	-	-
	+5	943	1630-2810	3231	119	3350	1499	75 ± 20	3845 ± 88	- 495 ± 155	440 ± 74	-	-
	+6	1508	1630-2810	3540	188	3728	2029	129 ± 35	3479 ± 87	+ 249 ± 162	294 ± 74	+	+
	+7	2707	1630-2810	3104	328	3432	717	112 ± 30	3108 ± 100	+ 324 ± 169	47 ± 74	+	+
	+8	1924	1630-2810	2894	235	3129	927	93 ± 25	3765 ± 104	- 636 ± 167	295 ± 74	-	?

B5	-3 -2 -1 0 +1 +2 +3	890 773 782 840 707 1361 1557	1380-2540 1380-2540 1380-2540 1380-2540 1030-2140 1030-2140 1030-2140	3193 3039 2402 3543 2504 2728 2589	111 96 97 105 89 171 190	3304 3135 2499 3448 2593 2899 2779	1774 924 813 896 941 649 825	59 ± 20 59 ± 20 50 ± 20 59 ± 20 54 ± 20 117 ± 41 74 ± 26	3457 ± 75 3371 ± 90 2527 ± 75 4287 ± 109 2929 ± 81 2151 ± 93 2291 ± 77	- 153 ± 141 - 236 ± 153 - 68 ± 125 - 239 ± 182 - 336 ± 133 + 748 ± 151 + 498 ± 133	291 ± 72 350 ± 72 291 ± 72 332 ± 72 215 ± 70 38 ± 70 35 ± 77	- - - ? - - - - - - + + + +	? ? + - ? + + +
B6	-5 -4 -3 -2 -1 0 +1 +2 +3 +4	1063 1303 1340 1369 1340 1299 1270 1370 1187 1090	1860-3070 1760-2960 1640-2820 1640-2820 1640-2820 1640-2820 1540-2720 1540-2720 1540-2720 1540-2720	3763 4346 4199 3567 3795 3627 3345 3180 2602 2233	132 162 166 169 165 161 159 109 146 134	3895 4508 4365 3736 3960 3788 3504 3349 2748 2367	2516 2085 1970 1822 1856 1758 1815 2064 1822 1878	64 ± 20 81 ± 21 76 ± 20 93 ± 25 85 ± 23 85 ± 23 81 ± 22 81 ± 22 72 ± 20 64 ± 20	4320 ± 77 3670 ± 74 4225 ± 87 3890 ± 88 3942 ± 86 4107 ± 92 3770 ± 83 3894 ± 80 3534 ± 76 3080 ± 65	- 425 ± 155 + 838 ± 164 + 140 ± 174 - 154 ± 162 + 18 ± 165 - 319 ± 167 - 266 ± 153 - 545 ± 147 - 786 ± 131 - 713 ± 113	419 ± 76 378 ± 75 242 ± 74 282 ± 74 241 ± 74 228 ± 74 204 ± 73 190 ± 73 276 ± 73 228 ± 73	- + + ? + ? + ? + ? - - - - - - - - - -	? + + + + ? ? - - - -
B7	-6 -5 -4 -3 -2 -1 0 +1 +2 +3	1030 1050 1207 1137 1137 1137 1117 790 595 910	2180-3410 2060-3290 1860-3070 1860-3070 1860-3070 1860-3070 1770-2970 1770-2970 1670-2860 1670-2860	2825 4013 4241 4600 3871 3996 3558 2441 1547 1869	128 129 149 141 140 140 137 97 72 112	2953 4142 4390 4741 4011 4136 3695 2538 1619 1981	1703 2113 1278 1658 795 989 872 1018 802 868	49 ± 20 47 ± 20 79 ± 20 64 ± 20 73 ± 20 73 ± 20 51 ± 20 41 ± 20 31 ± 20 39 ± 20	2937 ± 66 4082 ± 80 3426 ± 85 4528 ± 99 2769 ± 81 2468 ± 71 1958 ± 68 2159 ± 64 1933 ± 63 2037 ± 64	+ 16 ± 125 + 60 ± 163 + 964 ± 173 + 213 ± 194 + 1242 ± 161 + 1668 ± 154 + 1737 ± 137 + 379 ± 115 - 314 ± 95 - 56 ± 103	304 ± 78 307 ± 77 528 ± 76 406 ± 76 297 ± 81 411 ± 76 199 ± 75 293 ± 75 316 ± 74 232 ± 74	? ? + + + + + + + + ?	+ + + + + + + + + + ?
B8	1 2	830 850	2100-3340 2100-3340	2988 2607	104 107	3092 2714	2502 2092	147 ± 34 135 ± 31	3789 ± 83 3060 ± 73	- 697 ± 145 - 346 ± 127	404 ± 80 409 ± 80	- - - ?	- ?
B9	1 2	765 800	2260-3520 2260-3520	3319 2847	95 100	3414 2947	2079 2034	144 ± 31 144 ± 31	4674 ± 106 3634 ± 86	- 1260 ± 174 - 687 ± 145	380 ± 80 403 ± 78	- - - -	- -

In two normal subjects, B8 and B9 who were fed for forty-eight hours on a low diet comparable to that received by the pneumonia patients under the ordinary régime, the water balances were negative on both days, in both subjects. This is the finding to be expected in the early stages of inanition when the glycogen stores in the body are being reduced.

Since all of our patients partook of a diet which was calorically inadequate and exhibited negative nitrogen balances, positive water balances, when they occur indicate without question an increase of the percentile water content of at least certain tissues. The interpretation of the water balances is, however, quite difficult since the water derived from the catabolized tissues should be considered. In the table is given our approximate estimates of the amount of water released from catabolized tissues made on the assumption that the negative nitrogen balance was derived from tissues containing 3.4 per cent of nitrogen and 76 per cent of water and the remaining calories from fat containing 10 per cent of water.† Insofar as these estimates be correct they would signify that the release and formation of water associated with the marked tissue catabolism was sufficient and often more than sufficient to account for the negative water balance frequently observed during the precritical period of lobar pneumonia.

Loss of Water by Skin and Lungs. The loss of water by way of the skin and lungs was greatly increased throughout the period of study, being most marked at the time of the crisis. At the time of the maximal loss of water from skin and lungs the urinary water was usually diminished. It is noteworthy that in Case B7 in whom there was salt retention and visible edema there was decreased loss of water through skin and lungs. The loss of water through skin and lungs in Case B5 was of the same order of magnitude, but B5 was a boy 26 kilos in weight as compared with B7 approximately 60 kilos in weight.

Water Intake. Our patients took large quantities of water during the febrile period and especially near the crisis. In the control subjects to whom water was deliberately forced to the point of discomfort, the water intake did not reach the amount which was

† The figures for the estimates of the water derived from body tissues have been obtained by use of the following equations:

$$W_{tis} = W_{ox.tis.} + W_{pref.}$$

where $W_{ox.tis.}$ is the water of oxidation of the tissues and $W_{pref.}$ is the preformed water held with the tissues.

$$W_{ox.tis.} = 2.58(N_u + N_f - N_i) + 1.071 F_b$$

N_u = Nitrogen output in urine (grams)

N_f = Nitrogen output in feces (grams)

N_i = protein intake (grams) \div 6.25

F_b = estimated consumption of body fat from Calt

$$0.76 (N_u + N_f - N_i)$$

$$W_{pref.} = \frac{\quad}{0.034} + 0.10 F_b$$

$$0.034$$

taken easily by our pneumonia patients. This we believe to be correlated with the increased percentile content of water of certain tissues in the pre-critical period. We interpret it as evidence of a demand in at least certain tissues for water.

Discussion. General discussions of water balance in health and disease are to be found in reviews by Rowntree¹⁸ and by Marriott¹⁹.

In attempting any correlation between the water metabolism and the serum changes which we observed in patients suffering with lobar pneumonia, it has been necessary to consider the relation between the total amount of water available for excretion in the organism and the total amount of water excreted. In the water available for excretion we would include the water entering through the ingestion of liquids and food, the water of oxidation, and the water released in the metabolism of body tissues. The total amount of water excreted consists of the water loss through the urine, feces, sweat, breath, sputum, blood removed for analyses and any other secretions leaving the body. The difference between the water available for excretion and the water actually excreted might be termed a *relative water balance* and thus could be regarded as a measure of the percentile water content per unit of body tissues. A relative water balance would thus differ from the water balance, as ordinarily used, in the fact that the water balance does not take into account the water released and formed by oxidation in the metabolism of the tissues. There is reason to believe that this quantity may be considerable where there is tissue destruction although our data will not enable us to estimate it with any certainty. Nevertheless, in spite of this uncertainty it would seem to us desirable to consider it with appropriate allowances for error.

When the water released from catabolized tissues is taken into account, there appears to be an increase in the percentile water content of at least certain tissues even on those precritical days when the water balance was negative. Obviously on the days when the water balance was positive, the percentile water content of the tissue was without doubt increased even though the water released from catabolized tissues be entirely neglected. At the time of crisis the negative water balance reached a magnitude which exceeded the amount we estimated had been released from the tissue catabolism. Thus our studies, as well as others in the literature, seem to indicate that during the later precritical period in pneumonia there is increase in percentile water content of at least certain tissues coincident with variable water balance. As to the time at which this change begins, evidence is lacking because observations early in the disease have not been obtained.

The tendency to an increase in the percentile water content of the body tissues during the precritical period of lobar pneumonia is in the same direction necessary to explain a dilution effect in the serum. However, our approximations would indicate that the

magnitude is not sufficiently large to account for the serum changes we observed. The decreased concentration in the serum electrolytes must, therefore, be attributed in part to other factors leading to a redistribution of water and electrolytes between the serum and the tissues.

Summary. The water balance has been studied for a few days before and after the crisis in a series of 4 cases of lobar pneumonia on the ordinary but measured intake and in 3 additional cases, 2 of whom received large amounts of sodium chloride by mouth and the other a high-caloric diet for two days. In the patients under the ordinary régime daily negative water balances were the usual findings before the crisis. The patients receiving large doses of sodium chloride exhibited either a decrease of the negative water balance or a positive water balance.

Our studies of the water balance furnish no evidence suggesting a percentile decrease in the water content of the body tissues before the crisis; on the contrary, they do furnish definite evidence of a percentile increase of the water content of the tissues on several precritical days.

The difference between changes in water balance and changes in the percentile content of water in tissue has been discussed.

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A STUDY OF HEMOPHILUS INFLUENZÆ.*

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IN September, 1926, the problem was started of grouping serologically *Hemophilus influenzae* by means of agglutination and precipitin reactions, and of testing the virulence of these strains, thereby to determine if there was any correlation between serologic grouping and strain virulence.

Preliminary Experiments. Twenty-eight strains of *Hemophilus influenzae* were isolated from cultures of the pharynx, sputum, pleural fluids and one spinal fluid. The virulence of these microorganisms varied when injected into the peritoneal cavity of mice. In eight strains, 1 billion microorganisms killed the animals within eighteen hours, and in two strains the fatal dose in this time was $\frac{1}{2}$ billion microorganisms. All these strains were considered virulent. The eighteen other strains, in which 2 billion of the microorganisms did not kill mice after seventy-two hours were considered avirulent. Immune monovalent sera were prepared in rabbits for eight of these virulent strains.

In January, 1927, a strain of *Hemophilus influenzae* was isolated from the sputum of a patient suffering with acute influenza, on the third day of the disease. One-eighth of a billion microorganisms of this strain, designated as the Hammett strain, killed mice within eight hours. Because this strain appeared unusually virulent for mice, it was tested in rabbits. One-quarter of a billion living microorganisms of this strain injected intravenously, killed the rabbit over night, and a pure culture of it was recovered from the lungs, peritoneal exudate, and the heart blood.

Experimental Work. A series of experiments was then started to test whether the pathogenic factor of this strain was a toxic agent, which might be demonstrated in the filtrates of cultures. Parallel experiments were conducted with other strains of *Hemophilus influenzae*, isolated from patients in the Philadelphia General Hospital. This work was divided in the following manner:

* A Thesis in Bacteriology. Presented to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(a) Cultural experiments and virulence tests with twenty-three strains of *Hemophilus influenzae* isolated from human sources.

(b) Experiments with culture filtrates of *Hemophilus influenzae*.

(c) Rabbit experiments.

(d) Biologic studies on *Hemophilus influenzae*.

(e) Serologic reactions with immune serum.

(f) Therapeutic tests of *Hemophilus influenzae* (Hammett strain) immune serum.

(a) **Cultural Experiments and Virulence Tests with Twenty-three Strains of *Hemophilus Influenzæ*.** 1. *Preservation of Stock Cultures of *Hemophilus influenzae*.* Because of the observation of workers¹ that *Hemophilus influenzae* quickly loses its virulence when kept on artificial media, a method of preserving the virulence of stock cultures was sought. The culture medium employed in this study was brown blood broth, that is, infusion broth of pH 7.6 to 7.8 to which approximately 7 per cent by volume of sterile defibrinated blood was added. This was then heated until the blood became a rich brown color. The medium was tubed and incubated at 37.5° C. to test its sterility before use.

When cultures were first isolated from patients or from animals, transplants were made every three or four days, but as the cultures became adapted to the medium, transfers were necessary only every three weeks. At the time of transplanting, the cultures were also tested for purity by plating on brown blood agar. Those used for experimental work were always kept in the brown blood-broth medium, at room temperature (18° to 20° C.). It was found, in the course of this study, that cultures of *Hemophilus influenzae* though virulent as long as grown in brown blood broth, when transplanted to a solid medium for four or five generations, became avirulent. When stock cultures were kept at ice-box temperature, loss of virulence was more rapid than at room temperature. In the two years that the Hammett strain has been under observation, it has lost little of its original virulence. The cultures of the Hammett strain reclaimed after animal passage, and also strains from other sources, have all been maintained in the same manner and have remained virulent.

Thus, the virulence of a culture of *Hemophilus influenzae* has been maintained over a period of two years, all strains studied being cultivated and stored in a fluid medium, that is, brown blood broth, at room temperature (18° to 20° C.). It appears that the important points in this method of cultivation are the composition of the medium and the temperature at which the cultures are kept.

2. *Virulence Tests.* In testing virulence, 0.2 cc. of a brown blood broth culture of *Hemophilus influenzae* was streaked on a brown blood-agar plate and incubated at 37.5° C. After eighteen hours the growth was washed from the plate with infusion broth, since it was found that an exposure of ten minutes to physiologic saline solution destroyed the virulence. The suspension was centrifuged

at low speed for a half minute to remove agar particles, and diluted to contain 1 billion microorganisms per cubic centimeter using infusion broth as the diluent. It was then injected intraperitoneally into the mouse. Estimation of the virulence of a strain was based upon the numbers of microorganisms and the time required to cause the death of the mouse. Of the twenty-three strains studied, thirteen were virulent and ten were avirulent.

(b) **Experiments with Culture Filtrates of Hemophilus Influenzæ.**

1. *Preparation of Filtrates.* Filtrates were obtained of the brown blood-broth cultures after growing the bacteria for eighteen hours at 37.5° C. After centrifuging the culture to throw down the heavy particles of the medium, the supernatant fluid was filtered through a Grade N. Berkefeld filter. For the Hammett strain, it was found that this filtrate would kill mice within eighteen hours when 2 cc. was injected intraperitoneally, and rabbits when 3 cc. was injected intravenously. Filtrates from the other strains had to be used in larger volumes to produce corresponding effects.

2. *Skin Reactions with the Culture Filtrate of the Hammett Strain.* The culture filtrate of the Hammett strain prepared as described above in dilutions of from 1 to 100 to 1 to 7000 for skin tests upon individuals volunteering for the study. Control tests were made with filtered brown blood broth and normal horse serum similarly diluted. Sixty individuals were tested using 0.1 cc. of the dilutions of filtrate injected intradermally. The results were read after six and eighteen hours. After forty-eight hours the local reactions had faded materially. The typical reactions consisted of an erythema or a pink papule around the point of injection, and at times the erythema was surrounded with a blanched area. An erythematous reaction of less than 5 mm. in diameter was regarded as negative. Table I shows the results of these tests, the measurements of the local erythema being recorded in millimeters.

In the first group of 60 nonfebrile patients in the hospital wards, 42 gave positive skin reactions, the remaining were negative, or gave positive reactions in the control. Several individuals who gave negative results gave histories of exposure to influenza patients in the 1918 epidemic without contracting the disease at that time. Others had had very severe attacks of influenza in 1918 and recovered. One of these individuals had had a typical attack of influenza in the epidemic of 1889-1890 and though thoroughly exposed in the epidemic of 1918 did not contract the disease. In the second group of 75 normal volunteers, representing students, interns, nurses and laboratory workers, 51 gave positive and 24 negative skin reactions, or approximately 68 per cent reacted positively.

The results of the foregoing experiments show: (1) In virulent cultures of Hemophilus influenzae there appears to be a toxic agent capable of causing death of white mice when injected intraperitoneally. (2) This toxic agent is not found in filtrates of avirulent

strains. (3) Culture filtrates of virulent strains of *Hemophilus influenzae* produced skin reactions in 68 per cent of humans when employed in dilutions up to 1 to 7000. This test seems to be analogous to the Schick or Dick test and appears to be of such a nature that it may be of value in determining susceptibility to infection with *Hemophilus influenzae*, and should be further investigated.

TABLE I.—RESULTS OF SKIN TESTS ON HUMANS, PERFORMED WITH FILTRATE OF CULTURES OF *HEMOPHILUS INFLUENZÆ* (HAMMETT STRAIN), THE READINGS BEING RECORDED IN MILLIMETERS.

Patient.	1 to 100.	1 to 1000.	1 to 2000.	1 to 3000.	1 to 4000.	1 to 5000.	1 to 6000.	1 to 7000.	Control.*
1	20 x 20	20 x 18	8 x 10	7 x 7	—	—	—	—	—
2	18 x 14	15 x 15	15 x 15	12 x 10	10 x 10	7 x 5	—	—	—
3	22 x 15	18 x 20	11 x 12	10 x 10	5 x 7	—	—	—	—
4	18 x 25	18 x 20	20 x 20	20 x 15	10 x 10	—	—	—	—
5	23 x 22	20 x 18	8 x 7	9 x 10	10 x 10	5 x 5	—	—	—
6	19 x 22	16 x 26	14 x 22	14 x 20	10 x 10	10 x 10	—	—	—
7	30 x 25	26 x 22	14 x 26	11 x 5	9 x 6	5 x 6	5 x 5	—	—
8	17 x 20	14 x 15	11 x 22	10 x 15	9 x 5	—	—	—	—
9	14 x 11	13 x 10	10 x 11	5 x 5	—	—	—	—	—
10	...	19 x 24	17 x 18	16 x 16	16 x 15	6 x 6	—	—	—
11	...	18 x 20	11 x 11	9 x 10	9 x 10	7 x 6	—	—	—
12	...	22 x 22	16 x 14	16 x 15	12 x 11	5 x 5	—	—	—
13	...	26 x 22	20 x 18	15 x 16	12 x 12	10 x 10	—	—	—
14	...	18 x 20	15 x 19	15 x 19	15 x 17	10 x 10	—	—	—
15	...	10 x 15	8 x 8	8 x 7	7 x 6	8 x 6	5 x 6	—	—
16	...	20 x 22	19 x 19	16 x 17	11 x 10	11 x 5	5 x 5	—	—
17	...	17 x 22	17 x 15	16 x 10	14 x 14	10 x 10	—	—	—
18	...	17 x 17	15 x 12	15 x 12	15 x 10	5 x 5	—	—	—
19	...	16 x 18	11 x 14	10 x 13	8 x 6	3 x 3	—	—	—
20	...	14 x 15	14 x 13	12 x 14	9 x 7	—
21	...	10 x 14	11 x 9	7 x 7	—	—
22	...	12 x 10	10 x 10	9 x 10	7 x 6	—
23	...	12 x 16	14 x 14	14 x 16	9 x 7	—
24	...	10 x 10	9 x 9	10 x 7	6 x 6	—
25	15 x 16	10 x 11	6 x 6	—
26	10 x 8	8 x 6	4 x 5	—
27	11 x 12	10 x 7	4 x 9	—
28	14 x 12	11 x 9	7 x 4	—
29	9 x 10	6 x 7	5 x 8	—
30	25 x 27	14 x 11	9 x 4	—
31	11 x 14	9 x 6	4 x 4	—
32	10 x 8	11 x 8	8 x 5	—
33	13 x 12	10 x 9	8 x 6	—
34	16 x 18	12 x 12	9 x 9	—
35	8 x 8	6 x 8	4 x 4	—
36	18 x 20	16 x 14	12 x 12	—
37	14 x 16	8 x 8	4 x 6	—
38	20 x 20	20 x 16	12 x 16	—
39	10 x 12	10 x 10	6 x 4	—
40	8 x 10	8 x 6	4 x 4	—
41	22 x 18	12 x 12	6 x 6	—
42	24 x 20	20 x 16	12 x 14	—

The figures at the top of the chart, that is, 1 to 100, 1 to 1000, 1 to 2000 and so forth, represent the dilution of the filtrate used in performing the tests.

* Control, uninoculated filtered brown blood broth and normal horse serum.

(c) **Experiments on Rabbits.** As mentioned previously, experiments were carried out on rabbits with *Hemophilus influenzae* (Hammett strain). Twenty-three animals were used, 8 for animal passages of the Hammett strain, 7 for culture filtrate injections, 6 for exposure in testing contact infection of animals. Two were used for the implantation in the abdominal cavity of sealed collodion sacs containing culture or filtrate of *Hemophilus influenzae*.

1. *Effects of Intravenous Injection.*

Protocols. RABBIT 1. Weight, 2100 gm. Injected with 5 cc. of the supernatant fluid from a centrifugated eighteen-hour culture, of the Hammett strain. The next day the animal was ill; on the fourth day dull and listless; on the fifth day it developed paralysis of the hind legs, diarrhea, and purulent conjunctivitis; on the eighth day the paralysis was very marked, accompanied by spasmodic movements, and the animal died several hours later.

Necropsy. The pleural cavity contained pus. There was an acute purulent pericarditis. The smaller bronchial tubes were filled with pus. The lungs had many small pin-point hemorrhages. There was an acute purulent conjunctivitis. The intestines were distended, the liver was dark and friable, and the kidneys were very pale.

Pure cultures of the microorganisms were recovered from the conjunctiva, from the bronchii of both lungs, from the pleural cavity and from the heart blood.

RABBITS 2 and 3. Weight, 2520 and 2780 gm. Injected with 1 and 2 billion respectively of living microorganisms (Hammett strain). The next morning, both rabbits were dead.

Necropsy. The lungs were hemorrhagic with serous exudate into the plural sac, the heart was pale and there were subcutaneous hemorrhages. The lower lobes of the lungs of both animals were more inflamed than the upper lobes. *Hemophilus influenzae* was recovered from the lower lobes of the lungs of both animals.

RABBIT 4. Weight, 3040 gm. Injected intravenously with $\frac{1}{8}$ billion living microorganisms. The next day the animal was quiet and listless. On the second day the animal developed bloody diarrhea and died. Pure cultures of *Hemophilus influenzae* were recovered from both lungs and the heart blood.

The foregoing experiments with Rabbits 1 to 4 inclusive show the pathogenicity of the Hammett strain for rabbits. One billion living organisms injected intravenously, killed in eighteen hours. Amounts as little as $\frac{1}{8}$ billion proved fatal to rabbits within forty-eight hours. Acute inflammation of the lungs was produced with pin-point hemorrhages, such as is frequently seen in humans dying of influenza. Acute dilatation of the heart at times accompanied by a purulent pericarditis was noted commonly. A serous exudate was constant in the pleural sacs; and *Hemophilus influenzae* was readily recovered in cultures from the heart blood and lungs.

2. *Effects of Subcutaneous Doses.*

Protocols. RABBIT 5. Weight, 2375 gm. Injected subcutaneously with 1 billion living microorganisms and intravenously with 1 cc. of culture filtrate (Hammett strain). The animal died on the third day.

Necropsy. The lungs and peritoneal cavity contained a serous exudate. The lungs showed pin-point hemorrhages. One side of the left lung was completely hemorrhagic. The heart was enlarged and there was pus in the pericardial sac. Pure cultures of *Hemophilus influenzae* were obtained from the peritoneal cavity, from the lungs, heart blood and liver.

RABBIT 6. Weight, 2640 gm. Injected subcutaneously with $\frac{1}{4}$ billion living microorganisms of the Hammett strain. Two days later a swelling developed at the point of inoculation. The next day the swelling extended over approximately four square inches of the abdomen. On the fourth day the swollen area opened at the point of inoculation. A small incision was made and cultures taken. These showed pure cultures of *Hemophilus influenzae*. By the eighth day the area of infection was extending and by the tenth day the abscess had broken down and a thick, yellow ropy pus exuded. On the fourteenth day the opposite side of the abscess was opened and allowed to drain. On the twenty-fourth day a pure culture of *Hemophilus influenzae* was obtained from the wound. In this animal a purulent ulcerating lesion from which *Hemophilus influenzae* could be cultured at will persisted until the death of the animal, eight months later. This experiment indicates that the *Hemophilus influenzae* organism when injected subcutaneously is not as rapidly fatal as when injected intravenously. Rabbit 6 was used for subsequent experiments.

3. Results of Experiments for Immunization.

Protocols. RABBIT 7. Weight, 2200 gm. Animal received subcutaneously $\frac{1}{4}$ billion killed organisms of the Hammett strain on the first, third, fifth and twenty-third days. Injections were not made between the fifth and twenty-third days because of loss of weight of the animal. On the twenty-fifth day $\frac{1}{2}$ billion killed organisms were injected subcutaneously. On the thirty-seventh day $\frac{1}{4}$ billion living organisms were injected subcutaneously. The agglutinin titer of the serum taken just prior to the injection of the living organisms on the thirty-seventh day was 1 to 160. The animal died eighteen days after receiving living organisms. It was ailing for several days with a small lump at the point of inoculation.

Necropsy. The lungs were hemorrhagic with dark pin-point hemorrhages throughout. A serous exudate was present in the pleural cavity, and the heart was much enlarged. Subcutaneous capillary hemorrhages were also present. Pure cultures of *Hemophilus influenzae* were recovered from the pus of the point of inoculation, from the lungs, the heart blood and the peritoneal exudate.

RABBIT 8. Weight, 3140 gm. Animal received subcutaneously $\frac{1}{4}$ billion killed organisms of the Hammett strain on the first and third days, and $\frac{1}{2}$ billion killed organisms on the sixth, eighth, tenth and twelfth days. On the fourteenth, eighteenth and twenty-second days, $\frac{1}{16}$ billion living organisms were injected subcutaneously, and $\frac{1}{4}$ billion on the twenty-fourth and thirty-first days. The next day the agglutinin titer of the serum was 1 to 320. The animal developed an abscess at the point of inoculation of the living cultures and was used for subsequent contact experiments. (See Section Four.) The rabbit died after sixty-eight days, presenting throughout this period an abscess at the point of inoculation. No autopsy was performed.

Attempts at immunization with the Hammett strain failed, apparently because of the extreme virulence of this strain. The animals lost weight and when inoculated with living organisms, even following previous inoculations with killed organisms, became infected, and finally death ensued.

4. *Infection of Normal Rabbits Through Exposure to Infected Animals.* Normal rabbits were placed in cages with rabbits previously infected with *Hemophilus influenzae*, to determine if spontaneous infection would occur in normal rabbits as a result of contact. By referring to Section three it will be noted that Rabbits 6 and 8 had as a result of experimentation developed chronic abscesses and hence were utilized in this phase of the work to determine if through contact with these rabbits normal rabbits might become infected. The procedure and the results of experiments were as follows:

RABBIT 9. A normal rabbit was placed in a cage with Rabbit 6. Two days later Rabbit 9 was listless and died nine days later.

Necropsy. The lungs were hemorrhagic with emphysemic patches at the edges. The small bronchi were filled with pus. The heart was enlarged and there was abundant exudate in the peritoneal cavity. *Hemophilus influenzae* was recovered from the peritoneal fluid, heart blood and lungs.

As a control, Rabbit 10, a normal rabbit was exposed to Rabbit 13 which had previously received 2 cc. of culture filtrate intravenously to see whether a normal rabbit would become infected from a rabbit receiving filtrate. After five days, no infection developed, in either rabbit. Rabbit 10 was then placed in a cage with infected Rabbit 6 and the result of this experiment was as follows.

RABBIT 10. A normal rabbit was placed in a cage with Rabbit 6. The animal appeared to be ill after two days and died after eleven days.

Necropsy. The lower lobes of the lungs were hemorrhagic and the upper lobes contained pin-point hemorrhages throughout. *Hemophilus influenzae* was recovered from the heart blood, and the lungs.

RABBIT 11. A normal rabbit was placed in a cage with Rabbit 6. Rabbit 11 died in ten days. At autopsy, it showed a serous pleural exudate with inflamed and hemorrhagic lungs. *Hemophilus influenzae* was recovered from the heart blood, lungs and pleural exudate.

The above experiments show that infection may be transmitted by contact when normal rabbits are exposed in the same cage with infected rabbits, the infection appearing in two days and death occurring within about ten days.

5. *Infection Occurring in Rabbits First Inoculated with a Sublethal Injection of Filtrate and then Exposed to Infected Rabbits with Open Lesions.* Since the experiments in Section Four shows that normal rabbits become infected when brought in contact with rabbits previously infected with *Hemophilus influenzae* and having open lesions, experiments were performed to determine if rabbits previously injected with culture filtrate would when brought in contact with infected rabbits, become infected. The procedure and results were as follows:

RABBIT 12. A normal rabbit after receiving 5 cc. of culture filtrate of the Hammett strain subcutaneously was placed immediately in a cage with infected Rabbit S.*

* As will be shown later, 3 cc. of culture filtrate of the Hammett strain injected intravenously killed in eighteen hours. However, it was found that rabbits withstood larger injections of culture filtrate subcutaneously without succumbing.

After four days of this contact, the animal developed an abscess behind the ear, from which *Hemophilus influenzae* was recovered in pure culture. The animal died on the eighth day after exposure. At autopsy, the lungs were hemorrhagic with small patches of emphysema and the heart was enlarged. *Hemophilus influenzae* was recovered from the abscess behind the ear, the lungs and heart blood.

RABBIT 13. Received 2 cc. of culture filtrate intravenously and was placed with Rabbit 8. He developed a purulent conjunctivitis and died on the fifth day. An autopsy was performed and *Hemophilus influenzae* was recovered from the conjunctivæ, lungs and pleural exudate.

RABBIT 14. The animal received 2 cc. of filtrate intravenously and was placed in a cage with infected Rabbit 6. After two days he was ill; death occurring on the seventh day. At autopsy, *Hemophilus influenzae* was recovered from the lungs, heart blood and pleural exudate.

The above experiments show that while normal rabbits exposed to rabbits infected with *Hemophilus influenzae*, became infected and died within ten days (Experiments 9 to 12 inclusively), that rabbits which had received a sublethal dose of filtrate became infected and died in approximately seven days. Since the culture filtrates contain no *Hemophilus influenzae*, the indication is that these bacteria were acquired by contact infection.

6. *Rabbits Receiving Lethal Doses of Culture Filtrate.* The lethal dose of filtrate of the Hammett strain was determined as follows. Three rabbits were injected with culture filtrate of this strain using varying doses.

RABBIT 15. Weight, 2150 gm. Injected intravenously with 2 cc. of culture filtrate (Hammett strain). The animal survived.

RABBIT 16. Weight, 2420 gm. Injected intravenously with 3 cc. of culture filtrate (Hammett strain).

RABBIT 17. Weight, 2415 gm. Injected intravenously with 5 cc. of culture filtrate (Hammett strain).

RABBITS 16 and 17. These died the day following the injections.

Necropsy. The lungs showed pin-point hemorrhages with a red serous exudate in the pleural cavity, a picture similar to the lungs of rabbits having had injections of living *Hemophilus influenzae* organisms. The heart and kidneys were pale, the liver soft and friable. All cultures from organs of these rabbits were negative for *Hemophilus influenzae*.

Therefore, since 2 cc. of culture filtrate did not kill and 3- and 5-cc. doses did kill when injected intravenously into rabbits, it can be concluded that 3 cc. was the M.L.D. of culture filtrate when injected intravenously.

7. *Immunization of Rabbits with Culture Filtrates of the Hammett Strain.* Three rabbits (18, 19 and 20) were immunized to the culture filtrate of the Hammett strain, giving sublethal doses at first, and increasing these doses, by giving three injections subcutaneously resting four days, and following with four courses of intravenous injections on three consecutive days and resting four days. The animals were bled and the serums of 18 and 19 gave a precipitin titer of 1 to 1280 and that of 20 of 1 to 640. Rabbit 18, immune to

filtrate when exposed to a rabbit infected with *Hemophilus influenzae*, did not become infected.

An effort was made to immunize a rabbit to heated culture filtrate. Culture filtrate heated to 100° C. for one hour was used.

RABBIT 21. Received repeated injections of heated filtrate, given in the same manner as described for Rabbits 18 to 20, was exposed to an infected rabbit with open lesions. At the time of exposure, the serum of this rabbit gave a precipitin titer of 1 to 40, the precipitin titer of this same rabbit before the series of injections being negative. Rabbit 21 became ill within three days and died in eight days. At autopsy, the small bronchi were congested, the lungs were hemorrhagic and there was a serous exudate in the pleural cavity. The heart was enlarged. *Hemophilus influenzae* was recovered from the heart blood, lungs and pleural exudate.

The above experiments show that rabbits can be immunized to unheated culture filtrate, and following immunization can be exposed to infected rabbits, without becoming infected. On the other hand, a rabbit receiving repeated injections of heated culture filtrate, when exposed to an infected rabbit develops the infection. It thus appears that heating a culture filtrate to 100° C. for one hour destroys its property of exciting protective antibodies in rabbits.

8. *Experiments with Culture Filtrates in Collodion Sacs.* A sealed collodion sac containing culture filtrate of the Hammett strain was placed into the peritoneal cavity of a rabbit. The experiment was performed in the following manner:

RABBIT 22. A collodion sac containing 3 cc. of brown blood-broth culture filtrate, freshly prepared, to which had been added 3 cc. of sterile brown blood broth was placed into the peritoneal cavity of the rabbit. Three months later, the serum of the rabbit showed a precipitin titer of 1 to 1280. Eight months later, the precipitin titer had fallen to 1 to 640. While the experiment was performed on only one rabbit, the opinion might be advanced that the toxic agent of the culture filtrate continued to remain active, in the collodion sac, and that the animal developed some immunity against it.

RABBIT 23. A collodion sac containing 4 cc. of brown blood broth *Hemophilus influenzae* culture (Hammett strain) was placed into the peritoneal cavity of a rabbit. The next day, the animal was dead. On autopsy, it was found that the rabbit died of acute peritonitis, and that the collodion sac had broken. Pure cultures of *Hemophilus influenzae* were recovered from the peritoneal pus, and the heart blood.

Conclusions on Rabbit Experiments. 1. For *Hemophilus influenzae* (Hammett strain) 1 billion living organisms injected intravenously kill rabbits in eighteen hours, and produce lesions similar to those found in humans dying of influenza.

2. Living organisms of virulent strains of *Hemophilus influenzae* are not as quickly fatal when injected subcutaneously as cultures injected intravenously, since chronic abscesses are formed in the former procedure from which pure cultures of *Hemophilus influenzae* may be recovered several months after the initial injection.

3. Attempts at immunization of rabbits with a virulent strain of *Hemophilus influenzae* failed, due to the pathogenicity of the organism. With the methods employed, the animals lost weight and local abscesses were formed when an attempt was made to administer living organisms. The agglutinin titer of the serum was only 1 to 320.

4. Normal rabbits may become infected when brought in contact with rabbits previously infected with *Hemophilus influenzae* and having open lesions.

5. Rabbits previously injected with a sublethal dose of culture filtrate, will, when immediately exposed to an infected rabbit, acquire the infection and succumb sooner to this infection than would a normal rabbit if exposed to an infected rabbit. The culture filtrate appears to contain a toxic agent, which promotes infection with *Hemophilus influenzae*, since infection took place sooner when a sublethal dose of filtrate was administered before exposure. The theory may be advanced that a toxic agent is present in culture filtrates of virulent strains of *Hemophilus influenzae* and that it may act as an aggressin to infection with the organism.

6. Culture filtrates of a virulent strain of *Hemophilus influenzae*, when injected intravenously into rabbits, can cause death. Parker² and Wollstein³ also found that *Hemophilus influenzae* produced a filtrable poison which was lethal for rabbits when injected intravenously.

7. Rabbits may be immunized to culture filtrates and when exposed later to infected rabbits, be immune to infection. Parker² also immunized rabbits to at least four or five times the M.L.D.

8. Culture filtrates heated to 100° C. for one hour previous to injection failed to immunize rabbits to the point of protection when exposed to infected rabbits. Parker² also found that filtrate poison when heated to 55° C. for one-half hour was partly destroyed, and when heated to 75° C. for one hour, or boiled for five minutes, over two-thirds the toxicity had been lost.

9. When a collodion sac containing culture filtrate was placed in the peritoneum of a rabbit, the serum developed a precipitin titer as high as 1 to 1280.

(d) **Biologic Studies on *Hemophilus Influenzæ*.** The biologic characteristics of all strains used in this study were determined, that is, the Hammett strain, the animal passage cultures of the Hammett strain and the strains isolated from other patients.

1. All strains plated to ascertain if the peculiar mouse-like odor was present gave positive results.

2. Hemolysis: Not any of the strains studied showed hemolysis in blood-broth cultures.

3. Litmus milk reactions: None of the strains studied gave any change in litmus milk after seven days at 37.5° C.

4. Association with *Staphylococcus aureus*: All strains studied

showed definite increase in the size of the colonies when grown in association with *Staphylococcus aureus* on red blood agar plates.

5. Indol formation: The Hammett strain and the animal passage strain originating therefrom all produced indol.

Of twenty-two other strains isolated from patients, fourteen produced indol, and eight were negative. Of the fourteen strains producing indol, only seven were virulent. The virulence of a strain and its ability to form indol are apparently not closely related.

6. Growth on plain infusion agar without blood: All strains were plated on plain beef infusion agar, pH 7.6, and none gave growth.

The above tests show that typical cultures of *Hemophilus influenzae* were used for the experiment, and, as has also been shown by Rivers^{4,5} that no biologic classification could be made of them. Table II shows the biologic characteristics of twenty-three strains of *Hemophilus influenzae*. The fifteen animal passage generations of the original Hammett strain gave the same cultural characteristics of the parent strain.

(e) *Serologic Reactions.* Each of the strains of *Hemophilus influenzae* included in this study was tested by agglutinative and precipitin reactions with immune serum (horse) of the Hammett strain. The technique employed in these tests was as follows:

1. *Agglutinative Reactions.* The agglutination technique followed was according to the method of Small and Evans.⁶ The cultures of *Hemophilus influenzae* were streaked on brown blood agar plates and these plates were incubated over night at 37.5° C. The resulting growth was washed off in infusion broth. The suspensions were first centrifugalized to throw down agar particles and then centrifugalized at high speed for forty-five minutes to sediment the bacteria. The supernatant fluid was decanted, and the sediment of microorganisms resuspended in infusion broth, and heated at 85° C. for one hour. The suspension was then standardized to 1 billion microorganisms per cubic centimeter and agglutination tests performed with immune serum diluted 1 to 200. This made the final dilution 1 to 400. The tests were incubated in a water bath at 50° C. for eighteen hours. Naked eye readings were made.

2. *Precipitin Reactions.* The precipitin technique used was according to the following method: Eighteen-hour brown blood-broth cultures were filtered through a grade N. Berkefeld filter and the filtrate was tested for sterility. Immune serum (horse) of the Hammett strain was diluted from 1 to 10 up to 1 to 2560. Equal amounts of culture filtrate was added to the diluted serum and the tests remained at room temperature for eighteen hours. Naked eye readings were made of the precipitation next morning.

Table II shows the precipitin and agglutinative reactions of the twenty-three strains of *Hemophilus influenzae* studied.

The homologous strain and each of its animal passage subcultures were all agglutinated by the immune horse serum of the

Hammett strain. Of the twenty-two strains from other patients eighteen were agglutinated and four were not agglutinated. Thus, there was a high percentage of immunologic relation of these strains studied.

TABLE II.—CULTURAL CHARACTERISTICS, PRECIPITIN, AGGLUTINATIVE REACTIONS AND VIRULENCE OF TWENTY-THREE STRAINS OF HEMOPHILUS INFLUENZÆ.

Strain.	Source.	Associated with Staphylococcus aureus.	Odor.	Growth on plain infusion agar.	Indol.	Litmus milk.	Hemolysis.	Agglutination with immune serum of the Hammett strain.	Precipitin formation with immune serum of Hammett strain.	Virulence.
Hammett	Sputum	+	+	-	+	-	-	+	+	+
F 1 . .	Sputum	+	+	-	-	-	-	+	+	+
F 2 . .	Sputum	+	+	-	+	-	-	+	-	-
F 3 . .	Sputum	+	+	-	-	-	-	+	+	+
F 4 . .	Sputum	+	+	-	-	-	-	+	+	+
F 5 . .	Sputum	+	+	-	+	-	-	-	-	-
F 6 . .	Sputum	+	+	-	-	-	-	-	-	+
F 7 . .	Sputum	+	+	-	+	-	-	+	-	-
F 8 . .	Sputum	+	+	-	+	-	-	+	-	-
F 9 . .	Sputum	+	+	-	+	-	-	+	-	-
F10 . .	Sputum	+	+	-	-	-	-	+	+	+
F11 . .	Sputum	+	+	-	+	-	-	+	-	-
F12 . .	Bronchoscopic sputum	+	+	-	+	-	-	-	-	+
F13 . .	Bronchoscopic sputum	+	+	-	-	-	-	-	-	-
F14 . .	Bronchoscopic sputum	+	+	-	-	-	-	+	-	-
F15 . .	Bronchoscopic sputum	+	+	-	+	-	-	+	-	-
F16 . .	Spinal fluid	+	+	-	+	-	-	+	+	+
F17 . .	Spinal fluid	+	+	-	+	-	-	+	+	+
F18 . .	Spinal fluid	+	+	-	+	-	-	+	+	+
F19 . .	Spinal fluid	+	+	-	+	-	-	+	+	+
F20 . .	Pleural fluid	+	+	-	-	-	-	+	-	-
F21 . .	Pleural fluid	+	+	-	+	-	-	+	+	+
F22 . .	Nasal culture	+	+	-	+	-	-	+	+	+
		23 +	23 +	23 -	15 +	23 -	23 -	19 +	11 +	13 +

The homologous strain and each of the cultures recovered from animal passage of this strain, gave positive precipitin reactions with its immune serum up to a dilution of 1 to 640.

Of the twenty-two other strains ten gave precipitin reactions with this serum and twelve gave negative results. In order to correlate the serologic reactions with the virulence of the several

strains, the results of the virulence test are set down in Table II for each strain.

It will be noted that eighteen of the twenty-two other strains showed agglutination. Of these eighteen strains ten gave precipitin reactions and all of these ten were virulent. Each of these ten strain gave positive precipitin reactions with the immune horse serum (Hammett strain) in dilutions of 1 to 160. None were higher.

Thus it would appear that the precipitinogens are present and are related to the toxic agent in the culture filtrate of virulent strains that agglutinate with the immune horse serum.

(f) **Therapeutic Application of Hemophilus Influenzæ Immune Serum.**

1. *Serum Preparation and Titration.* Because of extreme toxicity of the Hammett strain, this culture was selected to immunize a horse, in an effort to prepare an immune serum in quantities sufficient for adequate therapeutic tests in patients presenting clinical influenza.

In immunization of the horse difficulties were encountered due to the high pathogenicity of the organism. At first small amounts of killed microorganisms suspended in physiologic salt solution were injected subcutaneously. Later, living microorganisms were given subcutaneously. The injection of viable cultures subcutaneously produced abscesses and it was discontinued in favor of killed microorganisms suspended in unheated culture filtrate. Again with this combination, large abscesses were formed which when cultured were sterile for such bacteria as Staphylococci, Streptococci, or Hemophilus influenzae. After these attempts treatment was again instituted with killed organisms suspended in physiologic salt solution. After eighteen months the serum gave an agglutinin titer of 1 to 2560 and a precipitin titer of 1 to 640.

The protective value of the immune serum has been tested on mice as follows. Killing doses, $\frac{1}{8}$ billion organisms per cc. of the Hammett strain were given intraperitoneally, followed in thirty minutes by 2 cc. of immune serum. Experiments have shown that 2 cc. of immune serum has the value of protecting mice against five killing doses of the microorganism. Controls were run on these experiments to be sure that the quantity of organisms would actually kill.

The serum has also been tested in the same way with other strains that agglutinated with the immune serum and here high protection was also manifested.

Because of the demonstrable antibodies in this serum which are capable of protecting mice against lethal doses of Hemophilus influenzae, (that is, the Hammett strain, and other virulent strains which show positive precipitin against the immune serum) it was decided to apply it clinically in typical acute influenza to test whether it had any effect on the toxemia of this disease.

The serum has been collected from five bleedings of the horse,

approximately eight liters each and has been preserved in ampules and stored for further favorable opportunity for use. The horse is continued under treatment in an effort to maintain a high-grade of immunity.

2. *Therapeutic Use of the Serum.* Opportunity for such testing was limited to 3 cases of typical acute influenza of the respiratory type, and 4 of meningitis due to *Hemophilus influenzae*.

Case Reports. *Influenza, Respiratory Type.* Only 3 cases with typical acute influenza within the first forty-eight hours of the disease were available for serum treatment.

CASE I.—(Patient of Dr. Diehl.) Male, colored, aged forty-two years, complained of soreness throughout body, cough and expectoration, and extreme pain in the eyeballs. The attack occurred in the morning, accompanied by chills. In the afternoon, when brought to the hospital, he had a temperature of 102.5° F. and was acutely ill. Sputum cultures showed *Hemophilus influenzae* predominating, accompanied by *Streptococcus mitior*. The white blood cell count was 4300. A clinical diagnosis of influenza was made. Twenty cubic centimeters of influenza immune serum were given intramuscularly at 5 P.M. Next morning by 11 A.M. the temperature had dropped to 98.5° F., and the white blood cell count was 9800. For twenty-four hours, the temperature continued normal and the white blood cell count was 7500. The patient felt well and continued to feel so until discharged from the hospital ten days later. The noticeable point in the convalescence of the patient was the feeling of well being in contrast to the usual symptoms of weakness and depression following an attack of influenza.

CASE II.—(Patient of Dr. Lanyon.) Male, white, aged thirty years, employee in the hospital, complaining of soreness throughout the body, accompanied by chills and having a temperature of 103° F. A white blood cell count showed a leukopenia of 4000. Nasal cultures showed pure culture of *Hemophilus influenzae* and throat cultures showed *Hemophilus influenzae* predominating, accompanied by pneumococcus, Group 4 and *Streptococcus mitior*. Twenty cubic centimeters of influenza immune serum were given intramuscularly on the first day of illness. Next morning the temperature was normal, and the white blood cell count was 8500. The patient felt very well and continued to do so until his return to work. He also had none of the symptoms following influenza, such as weakness and depression.

CASE III.—(Patient of Dr. Lanyon.) A young adult male with a clinical diagnosis of influenza, accompanied by high temperature and a leukopenia. Twenty cubic centimeters of influenza serum were given on the first day of illness intramuscularly followed by recovery of the patient within twenty-four hours.

Meningitis Due to Hemophilus Influenzae. Four patients with meningitis were also treated. They were young children showing pure culture of *Hemophilus influenzae* in the spinal fluid. The immune serum was given intravenously and intraspinally, and although brief, temporary improvement was reported by the clinicians, all cases proved fatal. A fourth patient, an eighteen-month-old boy, showing pure culture of *Hemophilus influenzae* in the spinal fluid, was

treated with the serum. A trephine operation was performed and the spinal canal washed with serum. The serum was also administered intravenously. This patient lived for twelve days following the beginning of serum treatment. On the twelfth day the patient died.

The application of the antiserum in these few cases is presented simply as a matter of record and for the sake of completeness in reporting the work undertaken. No inference as to any possible therapeutic value is implied. Our purpose has been that of preparing a potent antiserum against a very virulent strain of *Hemophilus influenzae* and storing it in sufficient quantity to test it out in clinical influenza should this disease return in epidemic prevalence. Only in this manner can it be determined whether the clinical toxemia of epidemic influenza is in any way related to the toxic agents in cultures of *Hemophilus influenzae*.

Conclusions. 1. Virulence of strains of *Hemophilus influenzae* may be maintained by keeping the cultures in suitable fluid media at a room temperature of 18° to 20° C. Of the twenty-three strains studied thirteen were virulent, and ten were avirulent to laboratory animals.

2. Rabbits and mice succumb to inoculation with virulent strains of *Hemophilus influenzae*. They also succumb to injections of culture filtrates of virulent strains. Thus the toxic agent causing the virulence of the strain is found in the culture filtrate.

3. Normal rabbits exposed to infected rabbits become infected by contact and death ensues in ten days with characteristic lesions found at autopsy. It also appears that previous treatment of a rabbit with a sublethal dose of culture filtrate hastens the contact infection of that rabbit with *Hemophilus influenzae* when it is exposed to an infected rabbit.

4. Skin reactions may be performed on human beings with culture filtrate of a virulent strain, giving positive results with a dilution of 1 to 7000. This test seems to be of the nature of the Dick or Schick reactions, and might perhaps be used to determine susceptibility to infection of humans with *Hemophilus influenzae*.

5. Precipitin and agglutinin reactions have been performed on the twenty-three strains studied, using the antiserum prepared with the Hammett strain. Nineteen agglutinated, eleven of which gave a precipitin reaction with the immune serum. Only the strains that gave both positive agglutinin reactions with the immune serum and were also virulent gave precipitin reactions. Precipitin reactions apparently shows a strict parallelism to the virulence in strains of *Hemophilus influenzae*.

6. The serum of a horse immunized with a virulent strain (Hammett) was found to protect mice against four to five lethal doses of *Hemophilus influenzae*. A few trials of the serum in patients are recorded.

7. It would appear that infection with *Hemophilus influenzae* is in direct relation with the pathogenicity of the strain, and that the pathogenicity is dependent upon the association of the organism with a toxic agent which may readily be identified in culture filtrate.

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POOLED ADULT BLOOD SERUM AS A PROPHYLACTIC MEASURE IN A MEASLES EPIDEMIC IN AN INSTITUTION.*

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MEASLES is so common a disease and frequently so mild an infection that the laity, and even doctors and nurses, fail to show the proper respect for its dangers. In fact, the mild manifestations so frequently shown lead to a reprehensible laxity in the prevention of the spread of the disease. While it is true that the disease may be mild in its constitutional reactions, it is often a severe affection, threatening life as well as causing unfortunate complications and sequelæ. In children under one year, measles itself produces a very high mortality. In older children, up to four years of age, complicating pneumonias often cause death. Later, while the mortality rate is lower, other complications and sequelæ arise. Even if the disease should run a mild and uncomplicated course, it may lower the resistance to such a degree as to activate a more dangerous process, since there is a close relationship between measles and

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tuberculosis. In children with a latent tuberculosis, measles often provides the spark for the flare-up. Miliary or pulmonary tuberculosis may follow an attack of measles. Tuberculous adenitis and tuberculosis of the bones and joints may appear as a late development. Realizing, then, the serious consequences of this disease, it is obvious that the wilful exposure of children to the infection is fraught with tragic possibilities. Prevention of the disease, surely, is desirable. The first step toward this end is overcoming the ignorance of the public with educational propaganda. The second step is the development of a systematic method of prevention by medical science. What problems does this prophylaxis present?

One great problem in prevention of measles arises from the fact that many contacts occur during the preëruptive catarrhal stage when the diagnosis is yet in doubt. During those months of the greatest prevalence of measles there are always so many cases of cold, grippe and other catarrhal respiratory conditions, that it is impossible to make an accurate or dependable differential diagnosis until the more definite signs of measles become apparent. By that time, one case will have made contacts with many other children in school and elsewhere, and many of these developing the disease, will in like manner, transmit it to others; so that before much time has elapsed a large epidemic has developed. Even with the isolation of all cases diagnosed, spreading will not be checked because of these contacts made during the catarrhal stage. In large epidemics, the closure of the schools, places of amusement and churches would materially lessen the incidence, but apart from its impracticability, what of the children of preschool age and those massed in institutions, involuntary contacts before isolation can be carried out? For their safety, some method of definite immunizing value should be sought, in fact is being investigated now. The developments during recent years indicate that definite progress is being made. As the result of immunization, known contacts have escaped the disease entirely or have been partially protected as evidenced by extremely mild infections.

The etiology of measles has been studied by a host of observers, many of whom have reported the most diverse agents or factors as the possible causes of this disease. None of these factors has ever been proved the cause of measles. In more recent years, another group of factors has been brought forward, including a filtrable virus, a green-producing diplococcus, another diplococcus surrounded by a slight clear halo and a definite streptococcus. The green-producing diplococcus was first discovered by Tunnicliff¹ in 1917. This diplococcus she isolated from blood of patients ill with measles during the preëruptive and eruptive stages. She and her coworkers since that time have published the results of extensive researches made along this line.

In 1923, Corona² and his associates in Italy, reported the isolation of an anaërobic diplococcus. They also have made extensive researches with their organism obtaining results comparable to those of the Tunnicliff laboratory. Ferry and Fischer,³ in 1926, isolated a streptococcus which they claim as the cause of the disease. Degkwitz⁴ goes into the realm of ultramicroscopy, supporting a theory instead of a discovery, and believes that a filtrable virus is the cause. Other investigators support the filtrable virus theory, including Park,⁵ who feels that such a theory is more tenable on account of the long incubation period of measles. Therefore, at the present time, there are three schools of thought as regards the etiology of measles. It seems quite likely that two, at least, are working with the same factor, the difference in their results being due to the variations in procedure and interpretation of findings.

Measles, however, has been produced experimentally, both in man and animals, by the inoculation of infective material: blood, nasopharyngeal and tissue cultures which contain the infecting organism, whatever it is proved to be. Whether or not the inoculated type of measles is a truly typical disease as in almost all cases of so-called successful inoculation, the disease is seen in a modified or attenuated form, certainly it does confer an immunity against measles. Natural immunity is often seen in very young children, but persists for life in only a few. The immunity commonly seen in infants may be transmitted through the breast milk, but it seems more likely that natural immunity is transmitted from the mother to the fetus through the placental circulation during gestation. That even this is not infallible has been proved by reports in the literature of mothers, who although they had had the disease during pregnancy did not confer immunity upon their children, since they later developed measles. The duration of the natural immunity is variable and may not last beyond the first year of life. This fact gives rise to the large degree of susceptibility among children.

The aim of prophylactic measures has been to develop a method to decrease the susceptibles, which is possible by certain forms of immunization. Because of the short duration of passive immunity, active immunization has been attempted. This is called morbillization and the term "sero-attenuation" has also come to be used. Herrman,⁶ in 1914, reported his success in inducing a mild form of the disease in young infants by inoculating these infants by means of gently rubbing the nasal mucosa with nasal washings collected from measles patients just prior to the appearance of the eruption. He felt that the immunity developing as a result of the mild atypical disease thus produced lasted for some time, at least two years. Hiraishi and Okamoto⁷ attempted active immunization by small repeated doses of infected blood. Degkwitz⁸ injected cultures of conjunctival and pharyngeal secretions in order to produce active immunization. Nicolle and Conseil⁹ used a serovaccination method

using first convalescent blood serum followed by blood from patients with active measles. Other investigators have attempted active immunization by somewhat similar methods. Despite all these efforts, the present status of active immunization is still in the experimental stage and while it is hoped that the longer protective methods will soon be available, for the present the fairly assured protection of passive immunization should be tried.

There are several methods of passive immunization, the most widely used being measles convalescent serum. Weisbecker,¹⁰ in 1896, in Germany published the first report of measles convalescent serum which he used for active therapy of the disease. Cenci¹¹ seems to have been the first to use convalescent serum for passive immunization. A very great many observers have published their results with this method. This convalescent serum is procured from patients within ten days after defervescence of the disease.

On account of the necessarily limited supply of human convalescent serum, an endeavor is now being made chiefly by Tunnicliff and her associates to produce concentrated animal serum for general use. Of the various animals so far tested, goat serum seems to offer the least amount of reaction although horse serum also is used in the preparation of the antiserum as for other infectious diseases. So far, the sera either have not been satisfactory, or have been so limited in quantity, that they are not available for general use. As regards the convalescent serum in Philadelphia, a certain supply is available at the Philadelphia Hospital for Contagious Diseases, but only in a quantity to supply their own expected needs.

Silverman¹² recently reported very interesting results obtained by himself and others using convalescent serum in community epidemic. Through the local bureau of health, blood was collected from convalescent measles patients, by health officers or by the family physicians. By using the serum thus collected definite protection was afforded the susceptibles who seemed likely to develop the disease. By this means, as well as by the mechanical isolation, the particular epidemic was controlled. It is interesting to note, in passing, that the serum of Ferry and Fischer did not give Silverman satisfactory results.

It is a well-established fact, that one attack of measles usually confers a life-long immunity. It is reasonable to conclude, therefore, that the antibodies developed in the blood during an attack of the disease, will persist in adult life. If this be true, then the use of a serum of an adult who has had the disease, might be effective as a preventive measure. When, therefore, it became necessary to cope with an epidemic of measles which broke out among the children of the Southern Home for Destitute Children, the thought of using the pooled sera of the parents occurred to us.

During March and April, 1928, an epidemic of measles occurred in this Home. This outbreak was coincident with an epidemic of

the disease among school children of the Philadelphia area. The source of the outbreak in the home was quite apparent, as all of the children of school age attend the public schools. The extent of the epidemic in the city and the number of cases developing made it necessary to attempt to limit the spread of the infection. As it was impossible to procure sufficient convalescent measles serum, from our patients or elsewhere, to insure a dosage sufficient to protect the susceptibles, and as no measles streptococcus antitoxin or animal serum was available for immediate use, it was decided to use adult serum, the donors being parents of children in the Home.

In the epidemic with which we dealt, owing to the contact of our children with public school children, as well as with each other, ten children developed typical measles, between March 24 and April 11. Our total population at that time was 100 children. Forty-five children had had measles in the Home or gave histories of having had measles prior to admission. There remained in the institution 55 children who gave no history of having had measles, a large majority of whom were, therefore, susceptible. Our problem was to give protection to these children, if it were possible. To obtain an adequate supply of serum, volunteers from the parents of the children were called upon. Each donor was questioned for a history of measles and only those who gave a positive history were used. From each donor enough blood was put into a sterile test tube for a Wassermann test and the tube was properly labelled. Then as much blood as could be conveniently removed was run into an Erlenmayer flask, which was provided with a two-holed rubber stopper into which glass tubing was inserted. One set of tubing was bent at an angle and used for aspiration to increase the flow. To the other a needle with necessary rubber attachment was fastened. All apparatus was sterilized before use, and the blood was withdrawn under aseptic precautions. The blood was set aside in the refrigerator to clot and the serum later decanted, or when necessary, centrifugalized. All the Wassermann-negative and sterile sera were pooled and divided and poured into small vials.

Owing to the length of time necessary for collecting the blood, it was done on two different days, and each day's collection went into separate pools. The inoculations were made as soon as the sera was ready. The first collection immunized 35 children and the second collection immunized the remaining 20 susceptibles.

On April 15 and April 22, the 55 susceptibles were inoculated with 5 cc. of the pooled sera by injection into the buttocks. The children were graded according to contact with the children sick with measles and according to age; and those in closest contact, and next, the young children were inoculated in order named. No untoward reactions followed nor did any fresh cases of measles follow nor did any fresh cases of measles develop.

The following questions arise: had we reached the end of a self-

limited epidemic, or had the epidemic been limited by isolation and hygienic management, or was the absence of new cases due to the definite protection of the serum? In answer to the first, we must remember that the epidemic in the city was still going on, and that our apparently well children were going daily to the public schools. As to the second, although the cases of measles were isolated as soon as a definite diagnosis was possible, there still existed contacts within the Home of susceptibles with the early measles cases having catarrhal symptoms. It, therefore, seems reasonable to conclude that the prophylaxis by the injection of adult serum was effective.

On April 23, however, one child showed a rash not typically morbilliform in character, and had a slight rise in temperature, without however, developing any prodromal coryzal symptoms, or Koplik spots. This reaction first thought to be a serum (anaphylactic) reaction, proved to be German measles. Seventeen other cases followed between April 23 and May 1, 8 of whom had not been given the serum because of a proven positive history of a previous attack of true measles. These cases ran the brief course usual in German measles and showed all its characteristic symptoms; nor was there any difference in the course between the 10 who had received the adult serum and the 8 who did not. Two of the original 10 cases of genuine measles were included in the 18 who later had German measles.

Shaw¹³ states that in German measles the susceptibility varies in different epidemics, though it is usually low: about 30 per cent of the individuals exposed. He also states that one attack usually confers immunity for life, although second attacks have been reported. Since, therefore, the pooled sera which we used, probably contained relatively few antibodies against German measles, by reason of the dilution and original small amount present we were not disappointed at its failure to provide protection against German measles as well as it did against true measles.

The use of the serum of adults with a history positive for measles we considered as an original procedure but in looking up the literature it was found that Degkwitz¹⁴ had recommended it, and that von Torday¹⁵ had reported 116 injections with failure to obtain protection in only 12 cases. Reitschel,¹⁶ Jervill¹⁷ Hilsinger,¹⁸ Goebel,¹⁹ Kovacs²⁰ and Bivings,²¹ have all used such serum but in quantities of 20 to 30 cc., which was much greater than the amount which we used. Some reported successful protection, while in others a modified measles developed. In the Southern Home, the 55 susceptibles who received the serum intramuscularly have up to this time apparently been protected, although 10 of these children have had an attack of German measles.

It has been suggested by Hilsinger that the effect of inoculation might be due to nonspecific agents in the serum: This thought has

also occurred to us, although in our series of cases, not one case of measles followed the injection of the adult serum, although 10 cases of German measles did. Are we to assume then that the infective agents of measles are more susceptible to the nonspecific agencies contained in adult blood than the infective agents of German measles? It seems more likely to have been the result of an insufficient concentration of German-measles antibodies.

Summary. 1. Fifty-five susceptible children all of whom had been exposed to measles were inoculated with pooled (Wassermann-negative) adult serum. Those in closest contact and then the younger children were inoculated with the first blood collected, as probably greater risks.

None of the children receiving the serum developed measles; nor had attenuated or modified measles.

2. Eighteen children of the Institution later had attacks of German measles. Of these 10 had received the serum, and 8 had not. (The latter had a positive history of a previous attack of true measles.) Two of the children attacked by German measles, were among the original 10 who contracted measles between March 23 and April 11.

Conclusions. 1. Measles is frequently too carelessly considered by the laity and even by the medical man. It constitutes a grave illness in all children affected under one year of age; while in its complications, it threatens the health and even life of older children. In delicate and pretuberculous children, it often is an activator for the various forms of tuberculosis.

2. Despite the almost universal susceptibility of the disease, prophylaxis against it is worth the effort, since, if it succeeds only in delaying the time of the onset, many lives will be saved.

3. Although the etiology of measles is the subject of investigations of many talented workers, the specific infecting agent has not been convincingly demonstrated. Various sera have been experimentally collected, but have given indifferent results in clinical tests. The blood (whole and serum) of convalescent patients, however, contains specific antibodies, since its injection has given uniformly good results, either entirely preventing the disease or producing an aborted or attenuated form, which has nevertheless, produced a lasting immunity.

4. Since the amounts of convalescent serum are manifestly very limited, and since the disease spreads so rapidly and is difficult to control by reason of many unsuspected contacts, some more practical means of prevention should be tried. Considering that one attack of measles usually gives immunity for life, the serum of adults having had the disease presumably contains the antibodies. On this presumption, the injection of adult serum should help to prevent the spread of measles, particularly in an institution for children, who are at once confined and yet exposed to contacts.

5. In an epidemic in 1928 among the school children of Philadelphia, adult pooled serum, collected from the serum, collected from the parents of children in the Southern Home, was injected in 5-cc. doses to susceptibles in the Home, without the development of one case of measles even of an attenuated form. Apart from all the possibilities of chance which might have produced this result, the effect was so satisfactory that the use of pooled adult serum in similar outbreaks should be encouraged.

NOTE.—We wish to acknowledge our indebtedness to Miss Frieda Ward for collecting and preparing the serum.

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EOSINOPHILIA IN LIVER DIET.

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Introductory Remarks. In their paper of 1927, "A Diet Rich in Liver in the Treatment of Pernicious Anemia," Minot and Murphy¹ mention that they have frequently observed a marked eosinophilia in patients on liver treatment, and they say: ". . . within a few weeks after the diet was begun, the polymorphonuclear eosinophils occasionally increased to beyond 20 per cent, this increase persisting for many weeks."

This observation has been confirmed by many other clinicians, and short remarks on this finding are often met with in the mass of papers already published on the liver therapy.

But only a few authors who have studied the blood picture of the white corpuscles in connection with liver diet, are paying any particular attention to the eosinophilia. Watkins and Berglund² state that in their case the number of eosinophils began to increase after three weeks of treatment, and they take the eosinophilia as being due to overdosage of liver. In 4 patients, Whitby³ found eosinophilia to set in at a similar point of time in the treatment, and in mentioning this finding he gives some hypotheses as to its nature: "The eosinophilia seems to be a part of the patient's reaction to the treatment, and the transient nature of the phenomenon points to a parallel between the reticulocyte reaction and the increase in eosinophils;" later he says: "It is conceivable, therefore, that eosinophilia will be found to be another favorable prognostic sign;" and later: "If anything, the phenomenon is another point in favor of attributing the beneficial effect of liver to its action on the bone-marrow."

In a subsequent paper, however, Smith and Whitby⁴ report that they also found eosinophilia—amounting even to 61 per cent—in a series of young people convalescing after various diseases in whom liver therapy had been instituted. Consequent to the above-cited views they also take the eosinophilia in these convalescents to indicate a stimulating effect of the liver treatment on the bone marrow.

Later publications on the liver therapy, in which the treatment with liver extract becomes more predominant, do not mention any presence of eosinophilia. Ordway and Gorham,⁵ to be sure, do mention the occurrence of eosinophilia in their material, but it does not appear from their report whether this was observed in patients on liver diet or in patients treated with extract. Whenever the reports on extract-treated patients give details of the white blood findings, there is no evidence of eosinophilia.

Still, the occurrence of eosinophilia in pernicious anemia on liver diet is a peculiar phenomenon. For in pernicious anemia the general rule is that the polymorphonuclear eosinophils are reduced in number or lacking altogether.

Author's Investigations. As we thought that we had become aware of certain principal lines in this problem, we have tried to throw some further light on this question by going through our material of liver-treated patients with pernicious anemia. In 37 of our 54 cases we have differential counts which are serviceable for a survey, although they might have been made more frequently and more regularly. With a view to the present question, we have further treated a number of control individuals suffering from various diseases with liver in one form or other, and we have watched the white blood picture in these persons.

The differential counts are made on cover-slip preparations, and 100 cells are counted in each specimen. Six per cent eosinophils is taken as the upper limit of the designation: no eosinophilia.

As the development of eosinophilia in our experiments has proved to depend on the form in which the liver is ingested, our results will be mentioned in sequence as the results of treatment with: (a) Raw liver; (b) fried liver; (c) liver extract; (d) results of alternating or mixed treatment.

(a) *Treatment with Raw Liver.* Calf liver is used throughout. The liver was ground very finely and given in wafers or as a beverage together with orange juice. At first, in 1927, the doses were small, but the initial dose was soon increased to 200 or 300 gm. a day, and a similar or somewhat smaller amount was given as maintenance dose. All told, 22 patients were treated for longer periods with raw liver alone. A few of these have kept on taking raw liver, others have gradually turned to mixed treatment or to treatment with extract alone; finally, a few patients who were previously treated with extract, have, for the sake of experiment, been treated periodically with raw liver.

During the treatment there developed a marked degree of eosinophilia in the great majority of these patients. When the liver is given in large daily doses, the eosinophilia usually appears in about four weeks, although it may take a longer time in some cases. As a rule, the eosinophilia sets in rather suddenly and attains some quite high values: 20, 40, nay, even as high as 74 per cent has been observed in one of our cases (Table I). Once the eosinophilia has appeared, it may vary some in value from one examination to another, but otherwise it seems to keep up as long as the administration of raw liver is kept up—at any rate, we have seen it to persist in patients who were getting this treatment for about two years.

TABLE I (F.M.H.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Mast.	Treatment.
Aug. 25, 1927	57	41	1	1	0	Raw liver, increasing to 200 gm.
Jan. 9, 1928	29	18	43	4	5	
Feb. 4	9	13	74	4	0	
Mar. 31	27	27	44	2	0	
April 18	40	19	38	3	0	Liver extract corresponding to 300 gm. of liver.
June 24	
Aug. 28	57	10	24	10	0	
Dec. 22	56	25	17	2	0	Liver extract corresponding to 100 gm. + fried liver, 125 gm.
Mar. 9, 1929	63	27	6	4	0	
June 10	50	23	13	4	0	

As is evident from the examples given, the number of eosinophils is increased at the expense of the polymorphonuclear neutrophils, whose number is reduced correspondingly—not only in percentage but also in absolute value; for the slight leukocytosis that is seen in the beginning of the treatment does not continue later on.

As exceptional cases in which the eosinophilia failed to appear, or developed to a slight degree only, we may point out one patient who was treated with raw liver for one and a half years without the eosinophilia ever rising higher than to 10 per cent. He claims he has taken 250 gm. of raw liver a day, but as the rest of the clinical results have been less favorable in his case, we are not fully convinced as to the accuracy of his statement. In another patient, who came under treatment not so long ago, eosinophilia did not appear until after six weeks of treatment, and in the following weeks its values were only 8, 19 and 9 per cent.

Corresponding experiments were carried out on 4 control individuals with a daily dose of 250 gm. of raw calf liver. The clinical diagnoses of these 4 cases were: Chronic endocarditis, acute rheumatic polyarthritis, achylia, gastric ulcer. After about four weeks of treatment all 4 control individuals showed the typical development of a marked eosinophilia. Instances are given in Tables II and III.

TABLE II (K. A. H.).—DIAGNOSIS: CHRONIC ENDOCARDITIS.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
Dec. 28, 1928	53	32	6	9	Raw liver, 250 gm.
Jan. 5, 1929	79	14	4	3	
Jan. 11	60	27	8	5	
Jan. 21	55	20	19	9	
Jan. 29	48	15	34	3	
Feb. 5	44	16	37	3	
Feb. 15	31	21	43	5	
Feb. 25	60	18	13	9	

TABLE III (M. J.).—DIAGNOSIS: POLYARTHRITIS RHEUMATICA.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
Sept. 18, 1928	70	21	3	6	Raw liver, 250 gm.
Sept. 27	66	21	5	8	
Oct. 1	69	27	3	1	
Oct. 13	35	19	43	3	
Oct. 23	19	10	67	3	
Nov. 5	30	29	37	4	
Nov. 14	44	20	35	1	
Nov. 23	17	26	54	3	

(b) *Treatment with Fried Liver.* Calf liver is used throughout. The liver is fried but slightly so that it is brownish on the outside and reddish in the middle. The dosage has been 250 gm. a day. Only one case of pernicious anemia is treated in this way. The treatment was kept up for three months. There was no eosinophilia; the highest count was 6 per cent (Table IV).

TABLE IV (E.N.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Mar. 13, 1929	62	36	1	1	0	Fried liver, 300 gm.
Mar. 23	44	49	0	8	0	
Mar. 29	
April 3	80	15	0	5	0	
April 10	71	14	0	12	3	
April 23	58	27	6	8	0	
May 1	69	18	1	13	0	
May 8	67	24	1	8	1	
May 15	55	33	4	8	0	
May 22	60	35	0	10	1	
May 29	51	21	6	18	4	
June 5	54	38	1	7	0	
June 14	67	36	0	7	0	
July 1	61	32	3	4	0	

Three control individuals with the diagnoses: Pleurisy, gastric ulcer, and pleurisy, and 1 normal control individual were treated respectively four, two, two and a half and two months in the same way. Three of the 4 controls showed absolutely no eosinophilia (Table V). In the fourth control individual the count gave 0, 0, 6, 7, 3, 6, 9, 8, 9 and 3 per cent.

TABLE V (S.).—DIAGNOSIS: PLEURITIS.

Date.	Poly.	Lymph.	Eos.	Mono.	Treatment.
April 12, 1929	57	29	5	9	Fried liver, 250 gm.
April 19	63	30	1	6	
April 29	57	31	2	10	
May 5	66	29	1	4	
May 10	62	25	3	10	
May 17	65	32	1	2	
May 24	64	21	1	14	
May 31	60	31	0	9	
June 7	59	25	4	12	
June 15	65	27	2	6	
June 22	66	26	1	7	

(c) *Treatment with Liver Extract.* A smaller part of the extract employed is Liver Extract Lilly or some other extract, the chief part

is Extr. Hepatis (Medicinalco, Copenhagen). Usually the initial dose has corresponded to 300 to 600 gm. of liver. As a rule the maintenance dose has corresponded to 200 to 300 gm. of liver, but this dosage has not always been kept up.

Twelve of the patients with pernicious anemia have continuously been treated with extract alone. None of these showed eosinophilia to the same degree as was observed in the patients treated with raw liver, and most of them showed no eosinophilia (Table VI). Two patients showed a slight increase of the eosinophil count (up to 8 and 9 per cent); in 1 patient there was once an apparently accidental increase to 14 per cent; and 1 patient who has been treated and observed for twenty months, showed twice an apparently accidental increase in number of eosinophils amounting to 18 per cent and 27 per cent, respectively. This case, however, may hardly be considered pure, as on a later examination the patient states that he had substituted whole liver for liver extract during a period some time before; but reliable information on this point is not available at the present.

TABLE VI (E. F. L.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Aug. 19, 1928	Liver extract corresponding to 600 gm.
Aug. 20	31	66	0	2	1	
Sept. 15	63	32	0	5	0	
Sept. 24	59	35	0	6	0	
Oct. 6	50	46	1	3	0	
Oct. 10	Liver extract corresponding to 300 gm.
Oct. 30	55	35	2	8	0	
Dec. 15	38	50	1	11	0	
Mar. 8, 1929	46	47	0	7	0	

A single control experiment on a patient with phlebitis who got liver extract corresponding to 600 gm. of liver daily for two months, gave no eosinophilia.

(d) *Alternating or Mixed Treatment.* More than half of the patients have been subjected to a change in treatment, as a rule in this way, that they were first treated with raw liver and then gradually went on to get liver extract. But, as mentioned, a few patients who had previously been treated with liver extract, were now—for the sake of experiment—put on raw liver.

The results of these changes in treatment have been quite clear-cut when the periods of treatment have been sufficiently long and sufficiently straight. The eosinophilia has gradually subsided on changing from treatment with raw liver to treatment with liver extract. In some of these cases, the eosinophilia disappeared within

a few months (Table VII), in others it persisted for a longer period—up to six months—before it finally went away (Table VIII). Some of these patients may later show an apparently accidental eosinophilia on a single examination, but it is quite reasonable, we think, to regard this as similar to the finding we mentioned in a few of the patients treated with extract alone.

TABLE VII (P.S.R.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Feb. 1, 1928	52	45	3	0	0	Liver extract corresponding to 200 gm.
Feb. 10	45	48	1	6	0	
Feb. 13	Liver extract corresponding to 300 gm.
Feb. 20	67	21	5	7	0	
Feb. 27	53	35	1	8	3	
Mar. 5	38	57	0	4	1	
Mar. 15	64	22	4	10	0	
April 18	Liver extract corresponding to 200 gm.
June 19	58	30	3	7	2	
Oct. 1	71	24	2	8	0	Liver extract corresponding to 100 gm.
Dec. 6	48	41	2	9	0	

TABLE VIII (S.E.R.).—DIAGNOSIS: PERNICIOUS ANEMIA. DIABETES MELLITUS.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Nov. 9, 1927	64	32	3	1	0	Raw liver increasing to 200 gm.
Nov. 12	
Jan. 4, 1928	59	20	14	7	0	Liver extract corresponding to 300 gm.
Jan. 14	8	29	51	9	2	
Mar. 17	
May 9	60	21	11	8	0	
June 19	52	20	17	5	5	
Aug. 15	62	29	3	6	0	Liver extract corresponding to 200 gm.
Oct. 16	68	26	3	3	0	
Oct. 23	68	26	3	3	0	
Nov. 19	61	21	9	7	2	
Dec. 3	60	25	8	7	0	
Mar. 9, 1929	60	33	3	4	0	

When, on the other hand, the treatment has changed from liver extract to raw liver, eosinophilia has appeared after the usual period, about four weeks, of treatment (Table IX). In such cases, it should be pointed out, the eosinophilia appears at a time when the patient has long ago been compensated for his anemia.

TABLE IX (E.N.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Sept. 8, 1927	Raw liver, increasing to 200 gm.
Jan. 4, 1928	29	14	49	6	2	
Feb. 15	Raw liver, 250 gm.
Mar. 9	Liver extract corresponding to 300 gm.
Mar. 25	57	10	27	6	0	
June 19	43	25	21	9	2	Liver extract corresponding to 100 gm. + 1 liver dish weekly.
Aug. 1	67	12	11	10	0	
Aug. 30	Liver extract corresponding to 100 gm.
Dec. 21	68	23	5	4	0	
Mar. 7, 1929	59	31	1	9	0	

TABLE X (E.N.) —DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
April 22, 1927	53	40	5	2	0	Raw liver, increasing to 200 gm.
May 12	
Jan. 6, 1928	47	28	11	12	2	Liver extract corresponding to 200 gm.
April 18	35	24	31	10	0	
July 5	Liver extract corresponding to 200 gm.
Dec. 12	42	42	14	2	0	
Mar. 5, 1929	63	30	2	2	0	
June 5	59	25	20	6	0	

TABLE XI (H.H.).—DIAGNOSIS: PERNICIOUS ANEMIA.

Date.	Poly.	Lymph.	Eos.	Mono.	Myelo.	Treatment.
Jan. 12, 1928	56	29	2	7	1	Liver extract corresponding to 300 gm.
Jan. 20	55	37	4	6	8	
Jan. 27	68	26	1	3	2	Raw liver, 300 gm.
Feb. 4	42	40	7	9	1	
Feb. 13	41	45	1	11	2	Liver extract corresponding to 200 gm.
Feb. 22	62	26	5	8	0	
Feb. 29	62	18	8	11	1	Raw liver, 300 gm.
Mar. 8	70	20	4	5	1	
April 3	Liver extract corresponding to 200 gm.
May 3	44	15	29	12	0	
May 31	Liver extract corresponding to 200 gm.
Aug. 3	47	27	17	9	0	
Sept. 4	70	14	13	3	0	
Dec. 18	53	15	26	6	0	
Mar. 4, 1929	66	21	8	4	0	
June 12	63	33	2	2	0	

If the patients have been taking a mixed treatment, partly raw liver, partly fried liver and partly liver extract, either combined or alternating, the eosinophil features will be somewhat "muddled" (Table X).

Discussion. As far as we can see, our investigations demonstrate two points: (1) That eosinophilia, at least in its typical pronounced form, develops only when the treatment is carried out with *raw liver*, and fails to appear on administration of fried liver or liver extract; (2) that this eosinophilia is not characteristic of patients with pernicious anemia, but appears *in other individuals too* on administration of the same quantity of raw liver.

As to the first of these points, it is quite true that treatment with underdone, fried or roasted, liver or with liver extract occasionally is associated with an increase in the number of eosinophils that approaches or exceeds the upper limit of the normal, and that instances of transitory and apparently accidental eosinophilia occasionally occurs in cases treated with liver extract, but this does not alter the main point: that the typical pronounced and persistent form of eosinophilia is encountered only in treatment with raw liver, where it is a very frequent, almost constant, phenomenon.

It is not so easy to say whether we disagree with other investigators on this particular point. For other investigators who mention the eosinophilia, in passing or more in detail, have evidently not paid any attention to this difference in effect of the various methods of administration, and for this reason they do not always state in which form the liver was given. Evidently Whitby has used both raw and prepared ("cooked") liver, and Smith and Whitby mention only "fresh-cooked" liver.

From the control experiments it is obvious that the phenomenon is not characteristic of pernicious anemia, as all the controls turned out positive. This finding suggests by itself that the eosinophilia is no indication of the therapeutic liver effect in pernicious anemia in the same way as, for instance, the reticulocyte reaction. And this conclusion is obvious from the fact that the phenomenon does not appear in treatment with fried liver or liver extract that, therapeutically, has given excellent results, with typical reticulocyte reaction and rise of hemoglobin percentage and erythrocyte count. Even when the doses of liver extract were excessive—corresponding to 600 gm. of liver a day—there was no eosinophilia.

So when Whitby and Smith and Whitby classify the eosinophilia with the reticulocyte reaction as indications of the curative liver effect, we cannot subscribe to this view. On the contrary, *we have to look upon the eosinophilia as a practically accidental by-product in the treatment that has nothing to do with the curative effect.* It seems perfectly unreasonable when Adler and Schiff,⁶ after treating 2 normal individuals with "Hepatrat" and finding an increase in eosinophils to 9 and 5 per cent, declare that "diese Tatsachen

sprechen dafür, dass das Hepatrat ein ausgezeichnet wirksamer Leberextrakt ist."

At present we shall not enter into any discussion of what may conceivably be the cause of this eosinophilia but merely mention that, from direct clinical observation, it appears to represent a harmless phenomenon.

Summary. Eosinophilia in liver treatment of pernicious anemia has appeared in a marked and persistent form when the treatment is carried out with raw liver (calf) in large doses. As a rule, the eosinophilia has appeared rather suddenly after about four weeks of treatment, and it has reach to high degrees—20, 40, even 74 per cent. It seems to persist as long as the administration of raw liver is kept up. On treatment with fried liver (calf) or liver extract, the phenomenon has usually been absent; and when present in single instances, it was in a faint and transitory form.

Control individuals suffering from various other diseases have responded to the treatment in the same manner as have patients with pernicious anemia, as they constantly showed eosinophilia on ingestion of raw liver but not after intake of fried liver or liver extract.

This eosinophilia is to be considered a by-product in the treatment of pernicious anemia with raw liver that has nothing to do with the curative effect of the treatment.

As far as directly observable, the eosinophilia represents a harmless phenomenon.

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EOSINOPHILIA WITH SPLENOMEGALY.

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THE occurrence of marked eosinophilia together with enlargement of the spleen has been reported a few times in recent years. These cases are of considerable interest, both because of their rarity and because of certain difficulties in classification which they present. At this clinic we have recently observed such a case, both clinically and pathologically.

Case Report. On July 30, 1927, B. N., a man, aged twenty-three years, was admitted to the hospital complaining of pain in the chest, cough and night sweats. His family history was negative apart from the fact that his father was said to be suffering from cancer. The past history included an attack of jaundice at the age of eight years and diphtheria five years previously. He had had frequent attacks of tonsillitis.

A year and a half before admission the patient began to have pain in the left chest, aggravated by motion, coughing and deep breathing. No other symptoms were present until seven months before admission, when, following a tonsillectomy, he began to have a productive cough, fatigue and night sweats. The pain became more sharp and was also felt in the right chest. Four months before admission a diagnosis of pulmonary tuberculosis was made and temporary improvement followed a two weeks' stay in bed. Two weeks before admission he spat up about a cupful of blood.

Physical examination revealed a rather listless young man with pale skin and reddish hair. There were no abnormalities of the head and neck. The chest showed some dullness above the third rib on the left anteriorly, and a patch of râles at the inferior angle of the right scapula. The heart appeared normal. The spleen percussed definitely enlarged, but the edge was not felt. The deep and superficial reflexes were very active and a tremor of the hands was present.

The most interesting laboratory finding was the blood counts, which are charted below.

	July 30, 1927.	August 1, 1927.	Sept. 20, 1927.
Hemoglobin	75%	50%
Red blood cells	3,520,000	2,780,000
White blood cells	16,000	13,450
Polymorphonuclears	26%	48%	33%
Small lymphocytes	13%	14%	8%
Large lymphocytes	0%	2%	3%
Eosinophils	60%	30%	55%
Basophils	1%	0%	1%
Platelets	180,000	

The smear showed some variation in size and shape of the red cells. The most striking feature, however, was the fact that the eosinophils were practically all adult forms. Only about 1 per cent of them appeared immature. A large number of them were vacuolated.

The urine showed a small amount of albumin and occasional hyalin casts. Stool examination was negative for ova, parasites and blood. The sputum was twice negative for tubercle bacilli, yeasts and molds. The Giemsa stain showed large numbers of eosinophils. Culture of the sputum yielded a staphylococcus as the predominating organism, with also occasional pneumococci. Microscopic examination of a piece of deltoid muscle was negative for trichinæ. Roentgen rays of the chest showed enlargement of the hylus on both sides, with accentuation of the markings into both upper lobes, and some clouding at the right apex. It was thought to be most suggestive of tuberculosis. A basal metabolism done when the temperature was 100.4° was +35.

The patient was not seen again after the last blood examination on September 20, 1927. His local doctor reported on November 29 that he was weaker and losing weight, with a cough which could only be relieved by morphin. He died, January 4, 1928. An autopsy was done fourteen hours after death at his home, by Dr. George Mackenzie, after the body had been embalmed. His physician reported that prior to death he developed severe pain in his head and nearly lost his sight. Permission to examine the head was not granted.

Autopsy Report (Abstracted). The body is that of a young man in fair state of nourishment. The body has already been embalmed and is very rigid throughout. There is an abundant growth of red hair.

There is no free fluid in the abdominal cavity. The lower margin of the liver lies 9 cm. below the xiphoid and 9.5 cm. below the costal border in the midclavicular line. The anterior margin of the spleen does not project below the costal border, but palpation reveals considerable enlargement. The mesenteric lymph nodes are irregularly enlarged, some measuring up to 1.5 cm. in diameter. In the mesentery a calcified node measuring more than 1 cm. in diameter is noted. A small amount of fluid is present in the right pleural cavity. There are dense adhesions at the apices of both lungs.

Heart. The apex of the heart is formed entirely of the left ventricle. In the myocardium of the right ventricle is a small brownish mottled area. There is some thickening of the mitral valve at the free border. A thrombus, 0.5 to 1 cm. in thickness, lines practically the entire cavity of the left ventricle.

Lungs. Section through the apex of the left lung reveals some dark hemorrhagic spots. Numerous similar hemorrhagic blotches are found over the anterior surface of the right upper lobe. Considerable pigmentation is present.

Spleen. The spleen is very large and deeply notched on the anterior margin. It measures 16 by 10 by 6 cm. and weighs 510 gm. The capsule is smooth. In the embalmed state it is dark bluish red.

Microscopic. **Lungs.** Fibrous pleurisy and emphysema are present. The hemorrhagic spots seen in the gross are found to be areas in which the alveoli are packed with red cells and contain pigment-laden wandering cells. In the center of the areas the red cells predominate while at the periphery only a few red cells are seen and the alveoli are crowded with wandering cells, less filled with pigment. In these areas, the alveolar septæ are thickened and crowded with wandering cells and eosinophils and some organization is present.

Heart. A thrombus is adherent to the wall and scars are present in the myocardium which appear to be the result of small infarctions. In these areas eosinophils are abundant.

Spleen. The pulp is crowded with eosinophils which to a lesser extent are invading the Malpighian follicles. They are for the most part adult polymorphonuclear cells, but myelocytes are frequently found. The eosinophilic granules appear normal but frequently, especially in the myelocytes, are sparsely scattered in the clear blue cytoplasm. Large cells resembling myeloblasts occur.

Liver. In the dilated sinusoids are many eosinophils whose morphology is similar to those encountered in the spleen. Here also are found a few large cells resembling myeloblasts. Many of the portal spaces are infiltrated with lymphoid cells and eosinophils.

Lymph Nodes. Eosinophils are more abundant in some nodes than in others. They are most frequent in the medulla, less so in the lymph cords and rather rare in the peripheral sinuses. Here as in the spleen the cells are for the most part adult, yet myelocytes are frequent.

Bone Marrow. The bone marrow is very hyperplastic, the overwhelming majority of the cells being eosinophils in all stages of development. They are for the most part myelocytes. Megacaryocytes and myeloblasts are frequent.

The marked clinical resemblance of this case to pulmonary tuberculosis is interesting and apparently explained by the finding at autopsy of multiple hemorrhagic foci in the upper lobes of the lungs. The leukocytosis with enlarged spleen and moderate lymphadenop-

athy, together with the presence in several of the tissues of eosinophilic myelocytes, at once suggests that this condition may be a leukemia involving the eosinophilic system of cells. Yet, upon examining the blood smears one is struck by the maturity of the eosinophilic cells. It is difficult to find any that might be classified as myelocytes. One wonders if this is not rather an unusual response of the homopoietic system to some infective or toxic agent. A search through the literature yields reports of several cases rather strikingly similar to the present one and it seems probable that they all constitute a rare clinical entity.

The earliest similar case of which we are certain is that reported in 1912 by Stillman,¹ of a man complaining of vague pains and weakness who exhibited pallor, lymphadenopathy and splenomegaly. The white blood count ranged from 118,000 to 165,000 with 85 to 91 per cent eosinophils, 1.8 per cent of which were myelocytes. No parasites were found. The Wassermann reaction was positive. The patient was followed for only a month. The author classified the case as one of myeloid leukemia with predominance of the eosinophilic cells.

In 1919, Shapiro² reported the case of a diabetic, aged forty-eight years, who complained of weakness, cough and loss of weight and who had râles and dullness at the apices of the lungs, palpable epitrochlear and inguinal glands and an enlarged spleen. The white blood count rose from 15,600 to 236,000 with 48 to 86 per cent eosinophils and increasing numbers of myelocytes. The Wassermann reaction was 4+. No parasites were found. Autopsy showed no tuberculosis, but patches of pneumonia, a thrombus in the right ventricle and infarcts in the spleen. Microscopically, there was cellular conversion of the bone marrow with a predominance of eosinophilic myelocytes and myeloblasts and infiltration of the spleen, liver and lungs with eosinophilic cells. In this case also the author believed he was dealing with an eosinophilic leukemia.

In the same year Giffin³ reported the case of a man, aged thirty-one years with marked splenomegaly, slight lymphadenopathy and a leukocytosis of 21,800, 73.6 per cent of which were eosinophils. Following splenectomy, the leukocyte count rose to 97,200 and later to 211,000 with eosinophils from 79 to 90.7 per cent almost all of which were mature forms. The patient died four and a half years later of empyema. The spleen and lymph glands showed many eosinophils and a few eosinophilic myelocytes. The bone marrow at autopsy was hyperplastic with many eosinophils, the majority of them well developed.

Aubertin and Giroux,⁴ in 1921, reported the case of a cardiac who for the period of four years during which he was followed, showed a white count of 6900 to 26,000 with eosinophils up to 65.8 per cent, practically all of them adult cells. The spleen was slightly enlarged. No parasites were found and the Wassermann reaction was negative.

Death was due to heart failure. An autopsy was performed which, however, did not include microscopic study. They discuss the possible relationship of the condition to anoxemia.

In the following year McDonald and Shaw⁵ reported the case of a man, aged forty-six years, whose history included loss of weight and some gastric disturbance. His spleen was enlarged and the leukocytes numbered 34,000 with eosinophils 71.4 per cent, only 0.7 per cent of which were myelocytes. Following splenectomy, the leukocyte count gradually rose to 138,250 with eosinophils 79.3 per cent, of which 4.7 per cent were myelocytes. During this period, there was apparent clinical improvement. The spleen showed the presence in the pulp and sinuses of eosinophils and eosinophilic myelocytes with, to a lesser extent, invasion of these cells into the Malpighian bodies. They cite a case seen by Dr. Edwin Matthew of Edinburgh, of a girl, aged twelve years, with digestive trouble and a leukocyte count of 12,000 to 15,000 with 85 per cent eosinophils. No parasites were found and the spleen was not felt. Unfortunately, the case could not be followed. Ward,⁶ in commenting on the case described by McDonald and Shaw, tends to regard the eosinophilia as a response to some demand, and cites a number of earlier cases which he regards as similar. Perhaps chief among these is that reported by Malins⁷ of a woman, aged thirty years, with painful splenomegaly. Following splenectomy, the leukocytes rose from 10,000 to 50,000 and large polymorphonuclear cells were found to be actively phagocytosing red cells. There is, however, no apparent proof that these cells were eosinophils.

In 1923, Langen and Djamil⁸ reported the case of an asthmatic, aged thirty years, with a total white count of 12,400, 75 per cent of which were eosinophils, apparently all adult cells. The spleen was not palpable on admission, but later was felt two fingers breadth below the costal margin. On one occasion a vermifuge yielded 33 ankylostoma. On a purin-free diet, the percentage of eosinophils dropped from 85 to 51 per cent, later rising again with the addition of purins to the diet. They classify their case as an idiopathic hypereosinophilia.

In 1925, Böckelmann⁹ reported the case of a man previously infected with malaria and hookworm, who complained of dizziness, dyspnea, cough and hemoptysis. He had fever, hypertension and albuminuria. The leukocytes numbered 36,400 with 74.8 per cent eosinophils. The spleen was considerably enlarged. Searches for parasites yielded only trichocephalus dispar in the stool on one occasion. After six month's treatment with a purin-free diet, the patient was symptom-free, the spleen was no longer felt and the white blood count was 7040 with 15 per cent eosinophils.

The same year Schmidt and Weyland¹⁰ reported a case of acute fatal illness characterized by diarrhea, stiffness of the extremities, muscle pains and high fever. The total white blood count was

90,000 with 67 per cent eosinophils, all adult forms. The spleen was not felt. At autopsy small thrombotic vegetations were found on the mitral valve and also thrombosis of some of the smaller coronary arteries. The spleen was not enlarged, but showed a hyperplastic pulp filled with eosinophils. Many eosinophils were present in the interlobular stroma of the liver. The walls of the intestinal ulcers contained round cells and eosinophils. The histology of the lymph nodes suggested leukemia except that the eosinophils were adult forms. In the bone marrow the young forms were only slightly increased.

The same year, Bass¹¹ reported the case of a child, aged six years, who had been referred to him for examination prior to a sinus operation. She had been known to have an enlarged spleen at the age of two years. At the time of examination she was found to have moderate lymphadenopathy with enlarged spleen and liver. The white blood cells numbered 14,800 to 25,600, with adult eosinophils 37 to 64 per cent and eosinophilic myelocytes up to 6.3 per cent. No parasites were found. Soon after the child died of bronchopneumonia. An autopsy was not performed.

In 1927, P. Armand-Delille and Pierredon¹² reported the case of a child, aged thirteen years, who, for the five months during which it was observed, had a leukocytosis of about 35,000 with an eosinophilia of 76 per cent. The child had had malaria with a number of recurrences and at the time of observation was suffering from severe bronchial asthma. There was some cervical adenopathy and the spleen was felt three fingers below the costal margin.

Hodgkins disease may produce a somewhat similar picture. Krumbhaar¹³ reports a case in a young woman, aged twenty-eight years, with a rapidly fatal febrile course, where the leukocytes rose to 120,000 with as high as 90 per cent mature eosinophils and the bone marrow loaded with eosinophils.

It is difficult to say whether some of these cases should be classified as a true leukemia or as a hyperleukocytosis, but it seems likely that they, together with the case reported here, constitute a clinical entity having the following features:

1. Leukocytosis of varying degree with a very high percentage of eosinophils, practically all of which are adult forms.

2. Splenomegaly and a moderate degree of lymphadenopathy.

3. Following splenectomy a marked increase of the eosinophilia without, however, any corresponding change in the clinical appearance of the patient.

4. Apparently a decreased resistance to infection, so that death supervenes from intercurrent disease after a variable period of time.

5. At autopsy a hyperplastic bone marrow filled with eosinophils in all stages of development, and in the spleen and lymph glands not only large numbers of adult eosinophils, but also a few eosinophilic myelocytes.

Summary. 1. A case is reported with marked eosinophilia and an enlarged spleen. No parasites were found. Autopsy revealed a hyperplastic bone marrow filled with eosinophils and in the spleen and lymph nodes very many eosinophils and occasional eosinophilic myelocytes.

2. Similar cases are reported from the literature.

3. The belief is expressed that these cases constitute a clinical entity.

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DEPRESSED BONE-MARROW FUNCTION FROM THE ARSPHENAMINS.

(INCLUDING A TYPE OF SO-CALLED AGRANULOCYTOSIS.)

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THE condition, instanced by the following case histories, is comparatively rare. For some reason not well understood, no accounts of it are found before the year 1919, despite the fact that salvarsan was brought out by Ehrlich in 1910 and neosalvarsan in 1912. Labbe and Langlois (1919) first described this complication of arspnenamin treatment. I have found reports of 39 cases since then. Of these, 23 patients died and 16 recovered.

Case Reports. CASE I.—M. C., a female, aged thirty-three years, was admitted on January 25, 1925, because of vaginal bleeding. She had had 6 intravenous injections of nearsphenamin and 8 mercurial injections. The dates of injections were:

Date.	Neoarsphenamin, gm.	Date.	Mercury salicylate, gm.
June 4, 1924.	0.6	July 23, 1924.	1
June 8	0.6	Sept. 24	1
June 25	0.6	Oct. 1	1
July 2	0.6	Oct. 8	1
July 9	0.6	Oct. 22	1
July 16	0.6	Oct. 29	1
		Nov. 12	1
		Nov. 19	1

After the last mercurial injection, her gums became sore. At the time of admission, the gums were bleeding freely. On December 20, she began to bleed from the vagina. This had continued since with fever, fainting spells, weakness, headache, and bleeding from the nose. Her appetite had been poor. She had had no hematemesis. She had been constipated. She had not bled from the bowels. Shortness of breath and palpitation of the heart were present. She thought she had become more anemic. Her menstrual periods had always been regular and of normal duration. She stated that she contracted syphilis from her husband sixteen years before. She had six children.

Examination. Marked pallor, cyanosis of the lips, normal pupillary reactions and elevated temperature were noted. The gums were slowly oozing blood. Pyorrhea and many gold-capped teeth were present. One small posterior cervical lymph node was felt. The examination of the lungs and heart gave negative signs. The spleen was not felt. The lower edge of the liver was 3 cm. below the rib margin in the midclavicular line. The peripheral reflexes were hyperactive. There was no swelling of the legs. Vaginal examination was negative except for oozing of blood from the cervix.

Progress. January 31. The uterus was curetted and packed with thromboplastin-soaked gauze.

February 1. A blood transfusion of 200 cc. was done.

February 2: The patient was very weak and extremely anemic. This note was made: "Yesterday, there was oozing of blood from the gums. Today, bleeding from the gums and vagina has ceased. There is no purpuric eruption. There are no signs of local disease to account for patient's condition. There is a marked leukopenia affecting mainly the polymorphonuclear cells. She has the signs and symptoms of aplastic anemia. There is increase in the bleeding time and reduction in the blood platelets. There is no jaundice or other gross evidence of blood destruction."

February 4: Elevation of temperature continued. The patient was semistuporous. There was no further bleeding from the gums or vagina.

February 5: The patient had a chill and was very weak and stuporous. The packing was removed from the vagina. This was followed by a slight hemorrhage.

February 7. A transfusion of 325 cc. of blood was done. The patient grew progressively worse, despite this, and died on this date.

Laboratory Notes. Average Urine Analysis: Color, amber; reaction, acid; specific gravity, 1030; albumin, none; sugar, none; no pus; no red blood cells.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Lymph., per cent.	Myelo., per cent.
Jan. 20, 1925 . .	10	870,000	3200	22	78*	1
Jan. 31 . .	10	530,000	2900			
Feb. 2 . .	10	560,000	2800	12	88*	0

* The lymphocytes were small lymphocytes of normal morphology. No nucleated red cells were found.

Blood Platelets. February 2, 1925: 89,600 per c.mm.

Bleeding Time. February 2, 1925: thirty minutes.

Wassermann Test. The Wassermann reaction was moderately positive.

Comment, Case I. If we had been ignorant of the arsphenamin treatment this patient had received, we might have diagnosed her condition as acute idiopathic purpura hemorrhagica, because of the general picture, the thrombocytopenia, the prolonged bleeding time, and so forth. It is to be noted that she received no neoarsphenamin for four months before the onset of symptoms. However, she received mercurial injections at weekly intervals after her last injection of neoarsphenamin. It is well known that mercury is also to some degree a bone-marrow depressant. The anemia was initiated by blood loss from hemorrhage. The paralyzed or destroyed erythroblastic tissue no doubt failed to produce red cells to replace the loss. We have evidence sufficient in this case to say that an aplasia (physiologic at least) of the myeloblasts, the erythroblasts, and the megakaryocytes was present.

CASE II.—N. T., a male, laborer, white, aged thirty-three years, was admitted on August 3, 1925. His complaints were soreness of the mouth, eruption of the skin, fever and general weakness. He had been treated for syphilis by weekly intravenous injections of neoarsphenamin for six weeks. On July 20, 1925, after his fifth injection, he had swelling and tenderness of the gums, a papular eruption of the face with swelling and redness of the right eyelid. These symptoms were disregarded by his physician; no blood count was made, and a sixth and last injection of neoarsphenamin was given on July 29, 1925. After this, he felt feverish and very ill. The soreness of the mouth increased. He was admitted to the Medical Ward four days later.

Examination showed a young man acutely ill with fever, appearing moderately prostrated and without pallor or edema. A papular eruption was seen over the face and anterior chest. A blepharitis of the right eye with congestion of the conjunctiva was noted. The right pupil was slightly smaller than the left. The gums were swollen, red and tender. The lungs seemed normal. A faint systolic murmur was heard at the apex of the heart. The liver, spleen and kidneys were not felt. There was no lymphadenopathy. A tentative diagnosis of arsenical stomatitis, dermatitis and blepharitis was made. The patient was given sodium thiosulphate intravenously without improvement.

Progress. August 9: The patient was acutely ill. A few fine râles were heard at the base of the right lung.

August 10: The patient was slightly jaundiced. The liver dullness extended 18 to 30 cm. below the costal margin in the midclavicular line. An ischiorectal abscess was found. A possible septicemia was thought of.

August 11: The ischiorectal abscess was incised. Cellulitis about the sacrum was seen. Jaundice was increased. The liver was tender. Râles at the right base and the left apex of the lung were noted with prolonged expiration.

August 14: The pulse became weaker, respirations forced, jaundice deeper, and the patient died at 8 P.M. The patient's temperature was constantly elevated throughout his illness.

Laboratory Reports. *Urine:* The specific gravity varied from 1010 to 1024; albumin varied from a slight tract to a cloud. Many dark, granular casts were present.

Blood Counts. Hemoglobin, 73 per cent; red blood cells, 3,900,000 per c.mm.; leukocytes, 1000 per c.mm.

Differential Blood Count. Polymorphonuclear, 0; lymphocytes, 100 per cent; transitionals, 0; eosinophils, 0. The lymphocytes were of normal morphology. No nucleated red cells were seen.

August 9: The total leukocyte count was 3600 per c.mm., of these, 26 per cent were polymorphonuclears, 70 per cent lymphocytes, and 4 per cent transitionals. The lymphocytes were of normal morphology. No nucleated red cells were seen.

Blood Chemistry. August 9: Urea nitrogen, 92; creatinine, 9.5; sugar, 104 mg. per 100 cc.

Blood Culture. August 9: *Bacillus proteus* was isolated.

Necropsy. (Dr. John R. Paul.) There was marked jaundice of the skin, conjunctivæ, and all the internal organs. An area of cellulitis was present in the region of the buttock.

The liver weighed 2240 gm. The liver cells were greatly vacuolated, chiefly about the central vein of the lobule.

The spleen weighed 450 gm. The Malpighian corpuscles were well defined. Small hemorrhages were scattered throughout and many polymorphonuclear cells were present.

The heart showed only parenchymatous changes on microscopic examination, but no gross lesion. The pleuræ showed no lesions. The lungs showed passive congestion at the bases. Many alveoli were partly collapsed. A few contained blood and fibrin, but there was no inflammatory reaction.

The stomach, ileum and colon showed hemorrhagic gastritis, ileitis and colitis.

Parenchymatous changes were present in the kidneys and the adrenals.

The postmortem blood-urea nitrogen was 160 mg. per 100 cc. of blood. Postmortem blood culture gave the *proteus bacillus* in pure culture. The bone marrow was not examined. No enlargement of lymph nodes was found in any of the superficial or deep groups.

The anatomic diagnoses were: Diffuse papular dermatitis with ulceration and gangrene of buttock, bacteremia with *bacillus proteus*, hemorrhagic bronchopneumonia, hemorrhagic gastritis, ileitis, and colitis, and acute parenchymatous degeneration of the liver and kidneys.

Comment, Case II. This patient's bone marrow was apparently destroyed or paralyzed by neoarsphenamin. A profound reduction in the output of polymorphonuclear leukocytes occurred. His natural immunity against infection was seriously impaired. A septicemia by *bacillus proteus*, an organism usually nonpathogenic, followed. The organisms of the mouth cavity invaded his tissues. The patient had symptoms at least a week before his last injection which should have led his physician to investigate his blood picture. Some reduction in the differential percentage of granular cells no doubt existed at that time.

CASE III.—L. M., a colored female, aged twenty-three years, was admitted on August 29, 1924, complaining of sore mouth, sore throat and headache. The soreness of the mouth began four days before. There were marked salivation and painful gums, but no bleeding. Fever and anorexia with vomiting of all food, frontal headache, burning and redness of eyes were noted. She had several watery stools in the twenty-four hours before admission. The diarrhea ceased soon after admission. The previous medical history, family and social history were unimportant.

Since January, 1924, her menses had been profuse and prolonged (two to three weeks) and accompanied by backache. In July, 1924, she had been on our surgical wards because of uterine bleeding. Clinical examination at that time was negative and a diagnostic curettage was done. No radiotherapy was used. The report on the uterine scrapings was hypertrophic endometritis. The bleeding ceased. Her Wassermann reaction was found to

be strongly positive. She received 0.3 gm. of neoarsphenamin on August 16 and August 23, respectively. She was sick all week after the second injection (August 16, 1924) and the third injection made her much worse, marking the onset of the present illness.

Examination (on admission) showed a temperature of 103° F., a pulse of 124 and respirations of 36. There was jaundice of the sclerae and salivation. The gums and the oral mucosa were red, swollen and tender. The pharynx was injected. Slight cervical and epitrochlear adenopathy was noted. The heart and lungs were negative. The liver was enlarged and tender. The spleen was just palpable.

She was menstruating at the time of admission. She developed small ulcerations in the mouth (roof and left cheek) and several teeth became loose and were extracted as well as a piece of necrotic mandible. The temperature became normal September 15 after a typhoid-like course and a decline by lysis.

Laboratory Reports. *Urine:* The urine showed a trace of albumin and occasional hyaline casts.

Wassermann Test. The blood Wassermann reaction was strongly positive.

Blood Count. The blood counts were as follows:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Lymph., per cent.	Mono., per cent.	Myelo., per cent.
Aug. 29, 1924	55	3,300,000	5250	0	100	0	0
Sept. 1	3350	1	24	4	69
(Oxidase stain; granular cells, 64 per cent; nongranular cells, 36 per cent.)							
Sept. 12	55	...	5800	16	58	0	26
Sept. 20	65	...	6200	33	44	0	21
Sept. 27	9050	44	46	0	10
Oct. 8	6600	56	43	1	0

After an uneventful convalescence, she was discharged free of symptoms on October 14, 1924, after which she was seen in the medical dispensary, and also in the salvarsan clinic on the following dates:

November 1, 1924: She received neosalvarsan 0.3 gm. intravenously.

November 11, 1924: She felt well, although menstruating every two weeks but not excessively. The blood showed: Hemoglobin, 85 per cent; red blood cells, 4,440,000, leukocytes, 6800, neutrophils, 55 per cent; mononuclears, 5 per cent; lymphocytes, 37 per cent; eosinophils, 2 per cent; basophils, 1 per cent.

December 6, 1924: She was free of symptoms. The blood showed: Hemoglobin, 80 per cent; polymorphonuclears, 47 per cent; small lymphocytes, 36 per cent; large lymphocytes, 12 per cent; mononuclears, 4 per cent; eosinophils, 1 per cent.

December 17, 1924: She was given neosalvarsan 0.3 gm. intravenously.

January 15, 1925: She was feeling well but had a chill and felt badly for several days after the last dose of neosalvarsan. The blood showed: Leukocytes, 7200; neutrophils, 45 per cent; small lymphocytes, 49 per cent; large lymphocytes, 6 per cent.

January 22, 1925: She was feeling quite well. No blood count was made and she never returned and could not be located thereafter.

Comment, Case III. Although this patient had received no mercury, she had the general appearance of mercurial salivation. The prominent features were the swollen mucous membrane of the mouth with constant profuse dribbling of saliva, the depressed state

of the polymorphonuclear cells, and the constantly elevated temperature. It is questionable whether further arsphenamin therapy should have been attempted so soon after her severe illness. The danger of a further acute depression of the bone marrow even by small doses of arsphenamin was great. The presence of large numbers of myelocytes was interpreted as a stimulation myelocytosis.

CASE IV.—J. C., a white male teamster, aged nineteen years, was admitted on June 30, 1927, complaining of weakness and fever. He was well until February, 1927, when he had a chancre. Following this, he was given three intravenous arsphenamin treatments by his family physician. The exact date and dosage of this medication are unknown to me. There were no ill effects at the time of injection. He had no secondary syphilitic manifestations and felt well until April, 1927, when he developed quinsy on the left side. This was treated by incision and several days' rest in bed. The throat condition became well, but since this time (two months) he had not worked because of progressive weakness, fever, increasing pallor and chilly sensations. He had had no hemorrhages at any time. The past history was negative except for chancre as noted. The family and social history were negative.

Examination. This showed a well-developed young man markedly pale and quite toxic in general appearance. There was a generalized lymphadenopathy of slight degree. Nothing abnormal about the head was noted except cryptic tonsils. The lungs were apparently normal. The heart was enlarged. Systolic and diastolic basal murmurs and a Corrigan pulse were present. The spleen and liver were barely palpable. A tentative diagnosis of acute endocarditis was made before the blood picture was known.

Course. A typhoid-like temperature persisted until death occurred three weeks after admission. Blood cultures taken on June 30 and July 6, 1927, were sterile. A blood culture on July 18 was positive for *Bacillus pyocyaneus*. On July 2, a small bloodclot was expectorated. This was the only hemorrhagic feature. He showed no purpuric lesions during his course. The margins of the gums were infected and edematous but did not bleed.

Treatment. Blood transfusions were done on July 7 and 12, 1927. The transfusions did not improve his condition. Intravenous injections of tartar emetic (10 cc. of a 1 per cent solution) were given July 8, 9, 10, 12 and 15, 1927. No effect, good or bad, was noted. The patient died of toxemia on July 21, 1927. No necropsy was obtained.

Laboratory Reports. *Urine:* Urine analyses were negative.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Lymph., per cent.	Blood platelets, per c.mm.
July 1, 1927 . . .	30	900,000	30,000	100	270,000 300,000
July 5 . . .	20	950,000	52,300	100	
July 8 . . .	30	1,160,000	(After trans-fusion, 24		
July 10	1,075,000	59,200	...	
July 13 . . .	30	1,503,000	42,000	100	
July 19 . . .	25	1,503,000	60,000		

Oxidase stains failed to show granules in the mononuclear cells. Blood platelets on July 5, 1927, were 270,000 per c.mm., on July 10, 300,000 per c.mm.

Wassermann Test. The Wassermann reaction was strongly positive.

Comment, Case IV. The absolute absence of granular cells and the increase in lymphocytes is to be noted. Immunity was lowered to such a degree that the saprophyte, *Bacillus pyocyaneus*, gained entrance to the blood stream. It seems likely that this patient died from acute lymphatic leukemia. The influence of his arsphenamin injections from the point of view of etiology is problematical. The injection may have been merely coincidental. When the cause of acute lymphatic leukemia is fully understood, the connection may become clear. The literature records two cases similar from the point of view of great increase in leukocytes. Vill (1921) published reports of two young women who had received intravenous injections of collargol after preceding injections of neoarsphenamin. Both died from acute intoxication with hemorrhages, thrombocytopenia and purpura. In one patient there was a leukocyte count of 76,000, in the other 29,000 per c.mm. Vill considered the condition due to the selective action of silver on the reticuloendothelial system. Herzog and Roscher (1922) reported special studies on the same cases and arrived also at the conclusion that the condition was due to collargol poisoning.

CASE V.—M. H., a colored male, aged twenty-two years, admitted March 2, 1928, complaining of epigastric pain and jaundice. In September, 1927, he had a chancre. In April, 1928, he developed a secondary syphilitic skin eruption. He had no specific treatment until this time. Two weeks after the appearance of the eruption, he received his first dose of neoarsphenamin. He received injections of mercury and neoarsphenamin between this time and October 23, 1928, as follows:

Date.	Dose, cc.	
April 4, 1928	10.0	Mercodel.
April 8	0.6	Neoarsphenamin.
April 11	10.0	Mercodel.
April 13	0.6	Neoarsphenamin.
April 18	10.0	Mercodel.
April 20	0.6	Neoarsphenamin
April 25	10.0	Mercodel.
April 27	0.6	Neoarsphenamin.
May 2	10.0	Mercodel.
May 9	10.0	Mercodel.
May 11	0.6	Neoarsphenamin:
May 16	10.0	Mercodel.
May 18	0.6	Neoarsphenamin.
May 23	10.0	Mercodel.
May 25	1.0	Mercury salicylate.
June 6	10.0	Mercodel.
July 11	0.6	Neoarsphenamin.
July 18	0.6	Neoarsphenamin.
July 25	0.6	Neoarsphenamin.
Aug. 1	0.6	Neoarsphenamin.
Aug. 8	0.6	Neoarsphenamin.
Aug. 15	0.6	Neoarsphenamin.
Aug. 22	10.0	Mercodel.
Sept. 12	10.0	Mercodel.
Sept. 26	10.0	Mercodel.
Oct. 3	10.0	Mercodel.
Oct. 10	10.0	Mercodel.
Oct. 17	10.0	Mercodel.
Oct. 24	10.0	Mercodel.

One week after the last injection, he became jaundiced and suffered from vague epigastric pains, most intense three or four hours after meals and radiating along the left rib margin to the back. There was no vomiting. His urine was dark and smoky. His best weight had been 163 pounds. His admission weight was 140 pounds. There was no family history of blood dyscrasia. He had had measles and chicken pox in childhood, but had since been well.

Examination. Blood pressure: Systolic, 110; diastolic, 70. Pulse and temperature were normal. He was a well-developed young adult negro, aged twenty-two years. He did not seem to be very sick. There was deep jaundice of the sclerae. The pupils were equal and reacted normally. The nose was negative. The mouth cavity showed no abnormality except questionably diseased tonsils and two carious teeth. There was no thyroid enlargement and no cervical adenopathy. Examination of the lungs showed normal findings. Examination of the heart showed no abnormalities except a soft systolic apical murmur. There was slight epigastric tenderness. The liver, spleen and kidneys were not enlarged. The epitrochlear and inguinal lymph nodes were slightly enlarged. The peripheral reflexes were normal. There was no edema.

Laboratory Examinations. *Wassermann Test:* The Wassermann blood test was strongly positive.

Urine Examination. The urine contained an excessive amount of bile.

Stool Examination. Bile was present. No ova nor parasites were seen.

Blood Counts:

Date.	Hb., per cent.	R. b. c., per c.mm.	W. b. c., per c.mm.	Polymor., per cent.	Eosin., per cent.	Bas., per cent.	Lymph., per cent.	Mono., per cent.	Trans., per cent.
Nov. 11, 1928	97	4,450,000	4100	30	none	none	69	none	1
Nov. 30	9900	46	5	1	41	4	3
Dec. 7	6300	68	2	none	26	4	none

Course in Hospital. The patient was treated by rest in bed, general care and duodenal drainage. The jaundice cleared up rapidly. His general condition improved. He was discharged apparently in good health on December 8, 1928.

Discussion. This patient had an hepatitis precipitated by his antiluetic treatment. He also had undoubtedly a mild depression of his bone-marrow function. If he had received an additional dose of arsphenamin, I believe that he would have died from bone-marrow depression.

CASE VI.—K. C., a female, aged forty-four years, had a pelvic operation at the Frankford Hospital in March, 1928. At this time, she was found to have a positive blood Wassermann test, and was given intravenous injections of neoarsphenamin. The exact number of injections is not known. On July 27, 1928, she was transferred for further antisyphilitic treatment to the Outpatient Department of the Pennsylvania Hospital. She received intravenously 6 doses of neoarsphenamin, each dose being 0.6 gm., and the interval between doses a week. She was then given 12 intramuscular

injections of bichlorodol at weekly intervals. She then had a month's rest from treatment. On December 26, 1928, she was given 0.6 gm. of neoarsphenamin. On January 2, 1929, she complained of not feeling well. Her symptoms, however, were not definite enough to be disturbing, and she was given an injection of 0.6 gm. of neoarsphenamin intravenously, and 10 grains of sodium thiosulphate four times a day by mouth. On January 9, 1929, another injection of 0.6 gm. of neoarsphenamin was given.

About an hour after this injection, she began to bleed from the gums. She bled rather profusely for about eighteen hours, when the bleeding ceased. She "hawked up" a considerable amount of blood. At the same time, there was diarrhea with bloody bowel movements. She was prostrated and suffered especially from backaches. Her family physician who examined her at the time stated that she had a great many purpuric spots all over the body and that she lost such a large amount of blood that she was "bled white." The patient was so sick that she was afraid she would die. Her physician thought she would die from blood loss. She failed to report her condition to the Clinic; therefore, she was not followed until February 2, 1929. At this time, she seemed to have completely recovered and was doing her housework. A blood count was made on February 2, 1929, as follows: Hemoglobin, 65 per cent; red blood cells, 3,280,000; leukocytes, 6600; polymorphonuclears, 69 per cent; lymphocytes, 23 per cent; monocytes, 7 per cent; basophils, 0; eosinophils, 1 per cent.

The patient refused to return to Clinic for treatment.

Comment, Case VI. It is unfortunate that it was impossible to get blood counts on this patient until almost a month after the occurrence of hemorrhagic symptoms. The hemorrhages, the purpuric eruptions and prostration make it highly probable that there was a temporary depression of the bone marrow, affecting especially the blood platelets, with secondary hemorrhages from the mucous membranes.

The following case, with others showing leukemoid blood pictures in various clinical conditions, has been previously reported by Dr. E. B. Krumbhaar (1926). Through the courtesy of Dr. Krumbhaar it is included here in order that it may be more accessible as an instance of the rather rare condition under discussion.

CASE VII.—"Ha. I., a young married woman, aged twenty-one years, was admitted to the Philadelphia General Hospital, December 29, 1925, with acute gonorrhea and syphilis, both of which diagnoses were amply confirmed by history, examination and laboratory findings. Except for a slight general adenopathy and two carious teeth, there was nothing apparently germane to the present study.

"One month later, while her treatment was progressing satisfactorily (she had received a series of from 8 to 10 neoarsphenamin injections—Dr. H. F. Kotzen) her temperature, which had been practically normal, suddenly jumped to 102° F., and stayed rather constantly between 102° and 104° F. for nine days. A superficial ulceration was noted on the gums, which spread during the week and repeatedly yielded smears of Vincent's organisms (though not considered in every way typical). The submaxillary and submental nodes became slightly more enlarged, but the spleen was never palpable. On the eleventh day, the patient never having been more than slightly discommoded, except by the mouth ulcers, the temperature dropped quickly to normal, the ulcers soon healed and the patient has continued well ever since.

"Blood examination on the first day of fever showed a leukocyte count of 15,200, of which only 8 per cent were polymorphonuclears, 48 per cent lymphocytes and 44 per cent were doubtful large mononuclear cells which were eventually considered to be myelocytes. The next day the count had dropped to 4700 leukocytes with 60 per cent of the doubtful cells, and during the remainder of the illness the count remained between 3300 and 5600, distributed in a similar manner. On the day on which the temperature dropped, the count rose to 6300 and by the next day the special cells had practically disappeared. Although they reappeared later in small numbers, the leukocyte count remained about 6000 and the patient perfectly well until two months later March 28, 1926, when she eloped from the hospital.

"Blood Counts:

Date.	W. b. c., per cent.	Polymor., per cent.	Lymph., per cent.	Mono., per cent.	Eosin., per cent.	Bas., per cent.	Rieder cells, per cent.	Myelobl., per cent.	Myelocy., per cent.	Meta., per cent.	Hb., per cent.	R. b. c., per c.mm.
Feb. 2, 1926	15,200	8.0	48.0	44
Feb. 3	4,700	5.0	35.0	60	..	60	3,700,000
Feb. 5	4,700	6.0	41.0	53	..	63	3,550,000
Feb. 6	3,900	4.0	49.0	47
Feb. 7	5,600	1.0	52.0	3	44
Feb. 8	4,000	0.5	61.5	3	1	34
Feb. 9	3,300
Feb. 10	4,000	66	4,030,000
Feb. 11	6,300	32.0	55.0	13
Feb. 12	6,000	44.0	47.0	..	1	..	7	..	1
Feb. 13	6,800	40.0	60.0
Feb. 15	6,900	49.0	46.0	2	2	1	98	4,600,000
Feb. 16	6,100	59.0	39.0	..	1	1
Feb. 18	6,200	52.0	47.0	1
Feb. 22	8,000	65.0	28.0	5
Mar. 5	5,500	56.0	23.0	5	7	..	6	2	70	3,400,000
Mar. 12	5,300	40.0	44.0	2	3	1	80	..

Comment, Case VII.—"A blood sample taken during the height of the illness was shown to an unusually competent hematologist, who, on the basis of the blood picture coupled with fever and mouth ulcers, was strongly in favor of a diagnosis of acute leukemia. Subsequent clinical and hematologic developments, however, fairly rule this out."

General Discussion. The cases here reported belong to the group of symptomatic blood dyscrasias resulting from known causes. Benzol, radium and the Roentgen ray in excessive dosage may produce similar clinical pictures. Selling (1910) first called attention to the peculiar selective depressant action of benzol on the hemopoietic apparatus. The fact that benzol has such an action is of special interest when it is remembered that the arspnenamins are formed by the substitution of arsenic about the benzol ring.

It seems likely that arsenic is not the offending substance since arsenic poisoning does not usually produce a picture like that of the

group under discussion. However, a case of so-called granulocytic aplasia of the bone marrow following the use of an inorganic arsenic compound has recently been reported (1928) by Dr. Robert Y. Wheelihan, which seems of special interest in this connection. A child, aged nine years, with generalized involuntary twitching present since one month old, and thought to be caused by cerebral injury at birth, was given a total of 625 minims of potassium arsenate (0.41 gm. or 6 grains of arsenic trioxid) over a period of thirty days. She developed fever, inflammation of the pharynx, gingivitis and infected teeth. The liver, spleen and submaxillary lymph nodes were enlarged. The white blood cell count dropped from 14,400 to 1300 cells, with a decrease in the polynuclear neutrophils from 62 to 3 per cent, and a corresponding increase in the lymphocytes from 34 to 93 per cent. On the seventh day following onset of fever the temperature became normal, the white cell count rose to 8450 with 52 per cent neutrophils. The child recovered. Wheelihan states that this is apparently the first case on record with marked changes in the blood picture due to inorganic arsenic as such.

Recently, we have treated an unusually severe case of arsenic poisoning, a child aged nine years who had been given arsenic for ten consecutive months with resulting general edema, secondary anemia, wrist and toe drop. This patient had no depression of polymorphonuclear cells, no lowering of blood platelets, no hemorrhages, or other particular symptoms, found in these cases.

In the literature there are reports of blood dyscrasias following arsphenamin treatment under a variety of titles, aplastic anemia, purpura hemorrhagica, bone-marrow depression, agranulocytic angina, and so forth. All of these symptomatic depressions of bone marrow occur, dependent, no doubt, upon the degree of toxic action and the particular elements of the marrow suffering most injury. A general term, such as, "depressed bone-marrow function" seems desirable.

The condition is a rare one. During the past seven years, only 6 cases have occurred at the Pennsylvania Hospital. Coombes (1927) reports one case after four thousand injections of the arsphenamins. The condition does not seem to be due to unusual toxicity of a particular batch of the drug since it does not affect more than one individual, where many are receiving treatment from the same solution. It is possible that those individuals in whom depression of the marrow occurs possess congenitally, a weak hemopoietic apparatus. No proof can be found to directly support this. It seems probable that a depressed state of the marrow which also depressed natural immunity may exist for some time without symptoms until a chance infection reveals the situation. Secondary infection, no doubt, plays a large part in the destruction of the patient.

Reported cases indicate that no one type of arspnenamin is more apt to produce depression than another. Arspnenamin, neoarsphenamin, novarsenbenzol, sulpharsphenamin, silver arspnenamin seem to be equally potent in this regard.

A knowledge of the prodromal symptoms of acute aplastic anemia is of especial importance since the withholding of an injection of arspnenamin in a patient who has begun to show signs of bone-marrow depression, may save the patient's life. The mortality of the condition is very high after the symptoms become pronounced. A blood count, of course, is the most accurate check on the patient's condition, so that one who uses arspnenamin should know when to have a blood count made. Data on prodromal symptoms is scanty. Moore and Keidel (1921) state that itching, a mild macular, papular, or vesicular rash, prolonged fever or malaise, or any tendency towards purpura in a patient who has received arspnenamin, indicate that a blood count should be made before proceeding with the treatment. They also found an increase in eosinophils of from 5 to 8 per cent a warning sign. A slight decrease in the neutrophils is especially ominous. After a patient has shown symptoms of possible depressed bone marrow a long interval should elapse before further injections are made. No one knows how long this interval should be. A safe interval of time might be placed at a year, because of the extreme danger. Every patient who shows jaundice or unusual symptoms of any kind after arspnenamin medication, should have a blood examination before proceeding to the next injection.

The symptoms and signs of poisoning can be predicted from our knowledge of the pathologic physiology of the marrow. The arspnenamins do not always depress equally the various elements of the hemopoietic apparatus. Thus certain ones may fail to have hemorrhagic purpuric symptoms because the blood platelets have escaped, while at the same time there may be a profound anemia from the effect on the erythroblastic tissue. The lesion about the mouth and throat, and for that matter, inflammatory lesion elsewhere, such as bronchopneumonia, follow the destruction of the patient's active immunity. The exact site of origin of this immunity is unknown, but undoubtedly, ferments, originating in the polymorphonuclear cells, are an important part of it. When first seen, the patient's hemoglobin may be high and his blood platelets numerous. On the turn of the life cycle of the elements of the blood, the most desperate symptoms occur because the natural process of destruction of old and worn-out cells continues while the apparatus for supplying new cells has suddenly ceased to function.

While there is no specific treatment for acute anemia secondary to arspnenamin, there are certain logical indications for active therapy. Sodium thiosulphate may be given intravenously to attempt neutralization of remaining arsenic in the blood and tissues. This should be vigorously followed up and should be given as early as possible.

The lesions about the teeth and mouth should be treated by a dentist. Sodium perborate solution, 1 dram to a half glass of water used as a mouth wash is a very valuable solution.

Blood transfusions are indicated for the theoretical accomplishment of four objects of treatment: (a) To supply red blood cells and hemoglobin; (b) to supply polymorphonuclear cells; (c) to combat infection; (d) to supply soluble ferments probably decreased or absent from the patient's serum. Blood transfusions should be vigorously repeated. As many as 10 or 12 transfusions may be necessary, and this should be prepared for from the outset. It should constantly be kept in mind that the particular patient under treatment may not have an actual aplasia, but simply a temporary marrow depression, which stage may be tided over until the marrow is again able to supply the needed blood elements. One should not wait until the patient's condition is desperate to begin transfusions.

The most effective treatment no doubt is early recognition of the tendency to depression and the withholding of further antisyphilitic treatment until recovery of marrow function takes place.

Summary and Conclusions. Reports of seven cases of depressed bone-marrow function following arsphenamin treatment are detailed. The clinical pictures presented by these patients varied according to the degree of marrow depression and according to the particular element or elements of the marrow most affected. The cases reported belong to the group of symptomatic blood dyscrasias. It seems likely that the direct cause is disintegration *in vivo* of the arsphenamins, so that a benzol-like action takes place. This, however, is a matter of opinion and not of proved fact. The rarity of occurrence suggests a preceding weakness of the hemopoietic apparatus in the individuals affected. Careful blood examinations in patients showing unusual arsphenamin reactions should be made. Blood transfusions should be vigorously repeated in the treatment of bone-marrow depression, keeping constantly in mind that a physiologic paralysis rather than an actual aplasia may be present in the particular case, and that the patient may be tided over this phase to recovery.

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THREE ADDITIONAL CASES OF ACUTE HEMOLYTIC (INFECTIOUS) ANEMIA.

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IN 1925, 3 cases of rapidly developing anemia of an hitherto undescribed type were reported by the writer.¹ As was stated in that article, no reference could be discovered in the literature to similar cases, although general mention of acute anemias of a hemolytic nature was found. Since that time, however, several articles have appeared which describe cases simulating those which occurred in the experience of the writer. I. C. Brill,² Steffens³ and Benhamou, Jude and Gill⁴ report cases under the title of "acute febrile anemia." Moschkowitz⁵ describes a case of an "acute pleiochromic anemia, with hyaline thrombosis of the terminal arterioles and capillaries," and attempts to group it with those described by the writer. Comparison, however, fails to reveal the resemblance.

Holst⁶ and Christiansen⁷ report 2 typical cases. Holst believes that the disease bears no relationship to pernicious anemia. Christiansen's case did not respond to liver therapy and he quotes this fact as an additional argument against its relationship to pernicious anemia. This case recovered completely after long convalescence (two and a half months) without transfusion.

Since the last publication, the writer has had the opportunity to closely study 3 additional cases, and his attention has been called to 4 others. The 12 cases above mentioned presented similar clinical pictures and blood changes, and in 11 cases the disease was promptly arrested by transfusion. No sequelæ or fatalities occurred. The details of the 3 cases studied are as follows:

Case Reports. CASE I.—M. S., (Hosp. No. 115366) male, aged twenty-four years, has always been well, except for an occasional cold. His color has always been good. His occupation is that of civil engineer. Three days before admission to the Jewish Hospital of Brooklyn, after returning from a vacation resort in the mountains, he became feverish, his temperature rising to 104°, and persisting between 103° and 104°. His appetite disappeared and he noted a rapidly increasing weakness. Two days later he began to vomit greenish material. On the day before admission his skin became yellow and the urine became red in color. The physical examination showed a well-developed and well-nourished young man who appeared weak, with a marked icteric tint and pallor to the skin and mucous membranes. His temperature was 102°, pulse rate 100, and respirations were 20. His mentality was clear. The scleræ were deeply jaundiced. There was noted a soft systolic murmur at the apex which was not transmitted. The spleen was palpable at the costal margin. Examination of

TABLE I.—THE BLOOD PICTURE OF CASE I.

Date.	Time.	Hemoglobin, per cent.	Erythrocytes, millions per c.mm.	Color index.	Platelets, per c.mm.	Leuko- cytes, per c.mm.	Differential study.										Red cell study.						
							Poly. neut., per cent.	Poly. eosin., per cent.	Poly. baso., per cent.	Small lymphocytes, per cent.	Türk cells.	Mononuclears.	Promyelocytes.	Myelocytes.	Metamyelocytes.	Per 100 W.B.C.			Anisocytosis and poikilocytosis.	Macrocytosis.	Microcytosis.	Stippling, per cent.	Reticulocytes, per cent.
																Megakaryoblasts.	Normoblasts.	Free nuclei.					
8/16	9 A.M.	50	3.12	0.8	29,000	7	Marked	...	Mod.	..	8
8/17	9 A.M.	35	2.24	0.8	60.0	27.0	1.0	Marked	...	Mkd.	0.6	..
	11 A.M.	21	1.13	0.8	140,000	44,000	11.6	0.5	6.6	2.3	5.6	5.0	Mod.	Marked
8/18	4 P.M.	30	1.02	1.5	81.3	Marked	Many	8
	9 A.M.	20	0.99	1.0	13.5	1	2	1	1.5	4.0	3.0	1.5	7.0	Marked
8/19	4 P.M.	35	1.20	1.4	77.5	11.0	1	5	3.0	3.0	1.0	3.0	Marked
8/20	38	2.40	0.8	27,000	77.0	18.0	1	7	0.0	0.0	8
8/21	33	2.70	0.6	100,000	20,400	74.0
8/22	35	2.75	0.6
8/24	30	1.80	0.8	1	2	10.0	..	12	..	1.0	1.0	Mod.	...	Mod.	..	4
8/25	36	1.85	1.0	10,200	75.0	8.0
8/27	20	1.50	0.7	6,000	80.0	34.0	..	2	0.0	0.0	4
8/28	31	1.95	0.8	6,800	62.0	1	..	13.0	..	6	1.0	0.0	0.0
9/3	39	1.96	1.0	13,400	81.0	9
9/5	37	1.64	1.1	8
9/7	45	1.84	1.3	10,800	79.0	12.0	..	9	2
9/12	48	3.20	0.8	31.0	..	8
9/17	47	3.32	0.7	6,200	61.0	8
9/20	46	2.98	0.8	4	6
9/25	56	2.59	1.1	240,000	5,800	50.0	38.0	..	6
11/1	65	4.79	0.7	12,800	59.0	30.0	..	8	3.0

the blood showed a profound anemia, marked leukocytosis, and evidences of unusual hematopoietic activity. The details are noted in Table I. The urine contained a large amount of albumin and free hemoglobin, being of a thick, red, syrupy appearance. The course of the disease was very stormy. The anemia progressed at such an alarming rate that within twelve hours his hemoglobin fell from 35 to 21 per cent and his erythrocytes from 3,120,000 to 1,130,000 per cc. This was accompanied by an increase in the hemoglobinuria and jaundice. Fifteen hours after admission, a transfusion of 500 cc. of unmodified blood was given, with slight temporary improvement. The evidences of active blood destruction continued, and the patient became stuporous, the latter due probably mainly to uremia, and accentuated by cholera and profound anemia. Two more transfusions of 500 cc. of unmodified blood were done on the next day, but the patient became worse and lapsed into complete coma. During this time his temperature declined. On the fourth day after admission, he began to emerge from the coma, but his blood continued to manifest evidences of renal insufficiency for about three weeks (Table II). Of special interest are the high-retention values of all the metabolites studied, except the chlorids. Because of the severe hemoglobinuria, urobilinogen and urobilin estimations could not be done. Great difficulty was also experienced in the quantitative estimation of bile pigments in the blood serum because of the high degree of hemoglobinemia. The icterus index on the day following admission was 48. By the van den Bergh method, the direct reaction for bilirubin could not be read because of the hemolysis. By the indirect method, however, 5.5 units were calculated; on August 20, the icterus index was 24. Van den Bergh estimations could not be made because of hemolysis. On the twenty-second, the icterus index had dropped to 20 and the van den Bergh showed a slight delayed positive direct reaction, the indirect method yielding 1.5 units. Comment on these figures at this time is not made excepting to emphasize the fact that the calculation of icterus index was of greater value than the van den Bergh reaction to recognize and estimate the bilirubinemia. He gradually improved, evidences of blood destruction disappeared, signs of regeneration became abundantly evident, and he gradually recovered completely. Reexamination of the patient and his blood ten months later revealed no abnormality.

TABLE II.—BLOOD CHEMISTRY TABLE OF CASE I.

	Sugar, mg. per 100 cc.	Creatin- ine, mg.	Urea nitrogen, mg.	Uric acid, mg.	CO ₂ , volume per cent.	Chlorids, mg.	Diazo.
8/16	174	2.1	22.8	4.8	51.6		
8/18	272	59.4		
8/20	187	6.0	50.1	10.0	Neg.
8/22	150	10.0	50.0	10.0	
8/25	166	15.0	98.1	10.9	500	Pos.
8/27	166	15.0	80.4	10.8	500	Pos.
8/29	150	10.0	62.5	8.0			
8/31	150	6.0	83.3	7.5	Pos.
9/3	120	6.0	50.0	6.0			
9/10	103	3.5	31.2	6.6			
9/17	96	1.6	12.5	4.0			
9/20	100	1.7	13.1	4.3			

CASE II.—P. V., male, aged three years. Excepting for pertussis at eight months of age, he has never been ill. Two days before admission to

TABLE III.—THE BLOOD PICTURE OF CASE II.

[illegible]

the service of Dr. B. Kramer, he complained of abdominal cramplike pain and vomiting, the attack lasting several hours. This was accompanied by hemoglobinuria, and progressively increasing pallor. He appeared feverish (temperature 102.5°), drowsy and weak. Physical examination showed a well-developed and well-nourished child, with temperature of 102°, pulse rate 140 and normal respirations. The heart sounds were soft and rapid, and there was a soft systolic blow at the apex which was not transmitted. The tonsils were slightly enlarged but not congested. The abdomen was soft, the liver and spleen were not palpable. The blood picture is detailed in Table III and chart. The associated laboratory findings were as follows:

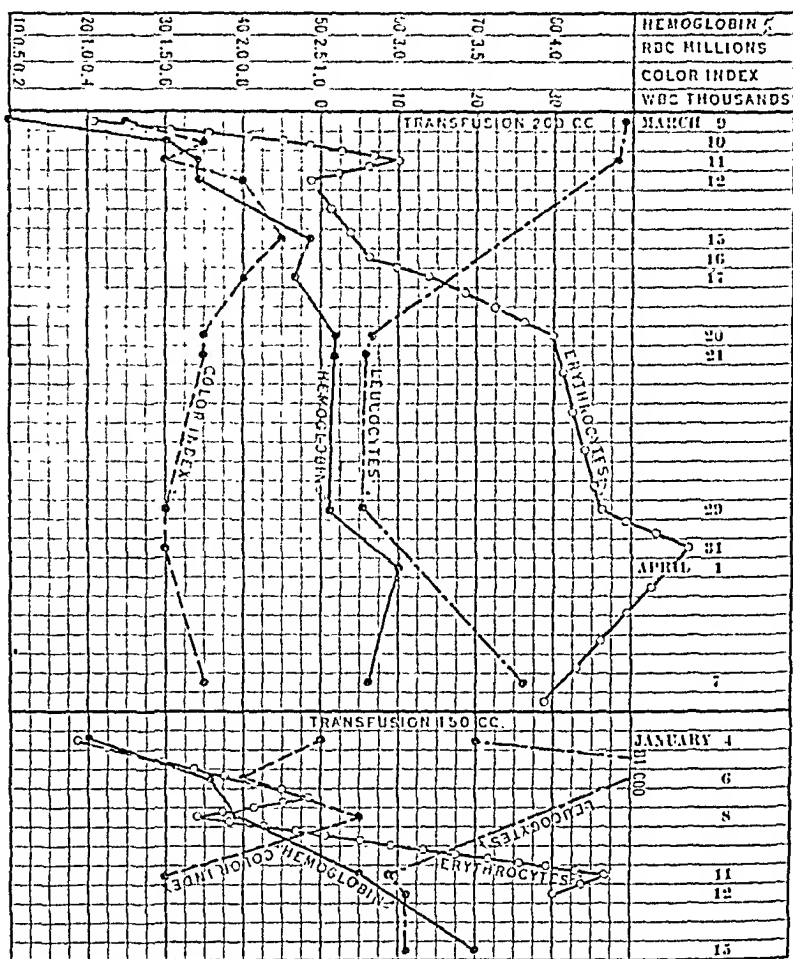


CHART.

bleeding time, 1.5 minutes; coagulation time, 3.5 minutes; platelet count, 300,000; tuberculin test was negative up to 5 mg. as was the Dick test; blood calcium, 10; phosphorus, 3; cholesterol, 236, and chlorids, 324 mg. per 100 cc. The blood Wassermann reaction was negative. The stools were negative for ova and parasites. As in the previous cases, on admission this case was one of marked anemia with evidences of pronounced bone-marrow activity. The urine contained large amount of hemoglobin. After a transfusion of 200 cc. of unmodified blood the hemoglobin rose from 10 to 34 per cent and the erythrocytes from 1,070,000 to 3,000,000 within a period of forty-eight hours. Within a week the hemoglobin disappeared

from his urine, and his recovery from the anemia was progressive. Three weeks later he developed an attack of acute tonsillitis, without recurrence of the anemia. He was discharged after four weeks, his physical examination showing a normal child with a normal blood picture.

CASE III.—A. T., male aged six months. The previous history was negative except for facial eczema from one to four months. He was breast-fed for four and a half months, now is on a formula.

Six days before admission to the service of Dr. B. Kramer, the child's appetite became poor. At the same time a persistent and increasing pallor of the skin was noticed. Two days before admission, he vomited some of his feedings, and since the onset has been irritable when disturbed, and apathetic when undisturbed. Physical examination shows a well-developed and well-nourished male child, with marked pallor of the skin and mucous membranes. There is an icteric tint to the skin and scleræ. He does not look acutely ill, but shows muscular hypotonia. The tonsils are moderately enlarged but not congested. The spleen is palpable one finger's breadth below the costal margin. The temperature on admission was 97.6°. The details of the blood pictures are shown in Table IV and chart. The additional associated laboratory findings were: bleeding time, 1.5 minutes; coagulation time, 2.5 minutes; platelets, 275,000. Gastric extraction shows a free hydrochloric acid content of 10 and a total acidity of 55. Fragility test-hemolysis began at 0.42 and was complete at 0.26 per cent salt solution. The Wassermann reaction was negative. Qualitative examination for urobilin in the urine was positive. Here, again, were the evidences of a profound, rapidly progressive anemia and accompanying active bone-marrow response. A transfusion of 150 cc. of unmodified blood was given on the day of admission, with an immediate improvement in the blood picture. In forty-eight hours the hemoglobin rose from 20 to 36 per cent, the red cells from 950,000 to 2,440,000. The subsequent improvement was slow, and a second transfusion of 150 cc. was done on the fifth day, following which, the hemoglobin rose to 55 per cent and the erythrocytes to 4,310,000 within seventy-two hours. Two months after discharge from the hospital, the child presented a normal blood picture, and physically the child was normal except that the spleen was just palpable at the costal margin.

Summary of Three Cases Previously Reported and Three Cases Now Presented. All 6 cases presented similar clinical and hematologic pictures, with certain variations. The age incidence was from six months to thirty-five years. Five were in males and 1 in a female. The history of onset in 3 cases was three days, in 2 cases, six days and in 1 case, two days. The onset in all 6 was characterized by the rapid development of pallor, icterus, weakness and rise of temperature. In 4 there was vomiting, diarrhea in 1, backache in 1, headache in 1 and hemoglobinuria in 2. On physical examination, 6 showed pallor and icterus, and 5 fever, while in 4 there was noted splenic enlargement and in 3 hepatic enlargement. The classical evidences of hemolysis were demonstrable in all. The peculiar blood picture described in the previous communication was common to all cases. In general, a very profound anemia, rapidly progressive, marked leukocytosis (a modified leukemoid picture: Krumbhaar⁸) and an erythroblastemia dominated the blood picture. The presence of megaloblasts, especially, is to be emphasized.

Careful and persistent questioning failed to elicit any history pointing to an agent that might explain the hemolysis. In one case it was thought the child might have swallowed a small amount of camphor, and in another there was a questionable history of sore throat. In neither could the facts in the histories be substantiated. Case I was complicated by manifestations of renal insufficiency. Although he became comatose, and chemical examination of the blood revealed nitrogen retention, his urine never contained leukocytes or casts. Apparently the condition was rather one of mechanical retention due to obstruction of the excretory apparatus of the kidney by the detritus from the enormous erythrocyte destruction. This is substantiated by the observations that the urine which he voided during the early part of his illness was thick and syrupy red, evidence of glucose retention and oliguria. This condition resembles, according to Wolbach⁹ a fatal form of hemoglobinuria occurring in horses known as azotemia.

The prompt cessation of the hemolysis after transfusion was just as striking as in the 3 previous cases, as was the rapid rise in the hemoglobin percentage and red cells. Reëxamination of all 6 cases, months after recovery showed no sequelæ or recurrences. Physically they are normal and blood examination reveal no abnormalities.

In view of Christiansen's observation of a recovery in his case without transfusion and the experience of the writer with two cases in adults, namely, cases B. L. and L. B. described in 1925, it appears that the cases may be divided into two groups. In one, the clinical course is rapid, the anemia developing with great speed and presenting an alarming clinical picture. This occurs especially in the infants. The other group is a group which runs a slower course and, as Christiansen puts it, is perhaps of a more benign character. The writer fully agrees with Christiansen that transfusion may not be necessary in all cases, but considering the precarious hematologic and clinical states of some of the patients studied, transfusion was considered an imperative procedure. In comparing the length of convalescence of Christiansen's case to the milder cases treated by transfusions there seems to be no question that transfusion hastens recovery to a marked degree.

All attempts to determine the excitant of the disease have been unsuccessful. In none has any history been elicited pointing to any of the usual or unusual causes of hemolytic anemias. The physical conditions of the patients on admission precluded any attempt to make any prolonged cultural investigation before instituting therapy in the form of transfusion, which has constantly terminated the process. Aërobic blood cultures have been uniformly sterile.

Conclusions. Three cases of an acute hemolytic anemia are described in addition to the 3 cases reported in 1925, and references to 2 others in the literature are included.

Eight cases in the literature conform clinically and hematologically to those described previously, 6 recovering permanently after transfusion of unmodified blood, 1 after transfusion with citrated blood (Holst⁶) and 1 without transfusion.

In two of the recent cases hemoglobinuria was present.

One case was complicated by uremia, due apparently to mechanical interference with renal function.

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ERYTHROBLASTEMIA OF INFANTS (VON JAKSCH'S DISEASE).

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IN 1889 and 1890 Rudolf von Jaksch¹ described an anemia of infants, characterized by deficiency in hemoglobin and in number of erythrocytes, marked anisocytosis and poikilocytosis, numerous nucleated red cells in the circulating blood, moderate and persistent increase of lymphocytes, and enlargement of the liver and spleen. This author also observed leukocytes containing phagocytized erythrocytes or fragments of erythrocytes. He suggested the name "anemia infantum pseudoleukemica" for this disorder. It is, however, commonly designated as von Jaksch's disease.

Charles Luzet,² in 1891, defined infantile pseudoleukemia as a disease peculiar to nursing infants, of unknown etiology, developing insidiously, characterized by severe anemia, enlargement of liver and spleen, large number of nucleated red cells in the blood, some of them in karyokinesis, and a moderate increase of leukocytes. Luzet regards the abundant erythroblasts and the mitotic erythroblasts as the outstanding features.

B. S. Denzer,³ in 1927, inclines to the view that the term anemia infantum pseudoleukemica of von Jaksch has been applied to various diseases of infants, some of which may well be placed in the accepted groups of secondary anemias and others more properly designated as true leukemias. He does, however, recognize the existence of a small group of infantile anemias which cannot thus be classified. These present anemia, splenomegaly, lymphocytosis and abundant nucleated red cells in the circulating blood,

The infantile hematopoietic system is obviously much more labile than that of the adult, as has been emphasized by Evans and Happ.⁴ It is probable that an agent, which would induce only an ordinary secondary anemia in the adult, might, in the infant, cause an anemia with abundant erythroblasts in the circulation. Erythroblasts are the normal blood cells in the earlier months of fetal life. They are commonly seen in the blood of newborn premature infants and are not regarded as abnormal in the newborn at full term. Hence, the peculiarity of the anemia of von Jaksch may depend essentially upon the infantile response. These authors regard rickets and other nutritional disorders of infancy as possible factors in the anemia.

T. B. Cooley⁵ has recently suggested that the term von Jaksch disease, be discarded. He regards the disease as an entity, characterized especially by the age of the patient and the large number of erythroblasts in the circulating blood, and prefers the designation, erythroblastic anemia.

During the past eight years, there has occasionally been admitted to the Babies Wards at the New York Post-Graduate Hospital an infant showing a blood picture such as that described by von Jaksch.

Case Reports. CASE I.—H. H., male, aged nine months, was born at full term, weighing 9 pounds at birth. Three older children in the family were well and the history of the parents was negative. The patient had been pale and jaundiced since birth. He was breast fed for three months and since then received modified cow's milk. He had no visible teeth and had never been able to sit up or to creep. Upon admission, the infant was pale and malformed, with a square head, prominent parietal bosses, short nose, malformed external ears, eyes of Mongolian appearance, protruding tongue, neck short and thick. Rachitic costochondral beading was evident. Liver and spleen were very large, the latter occupying nearly the left half of the abdomen. There was a slight umbilical hernia. The blood Wassermann test was negative. A diagnosis of Mongolian idiocy was made.

TABLE I.—BLOOD PICTURE OF CASE I.

	June 23	June 27	July 5	July 9
Red cells	2,344,000	..	3,080,000	2,368,000
White cells	19,800	14,600	16,100	14,100
Hemoglobin (in grams per 100 cc.)	6.1	..	8.3	7.3
<i>Differential Count (per cent).</i>				
Polynuclears	33	30	50	40
Small lymphocytes	4	15	3	46
Large lymphocytes	38	35	47	14
Mononuclears	11	3		
Transitionals	2	3		
Eosinophils	2		
Basophils	3	1		
Myelocytes	9	1		
Disintegrated cells	10		
<i>Nucleated Red Cells per 100 Whites.</i>				
Normoblasts	10	65	42	25
Microblasts	1	17		
Macroblasts	8	40		
Megaloblasts	3	3	1	

Blood examination on June 23 showed a marked deficiency in hemoglobin and erythrocytes (Table I). The nucleated cells observed in the leukocyte count numbered 24,000 per c.mm., but among these were numerous nucleated red blood cells, 10 normoblasts, 8 macroblasts and 3 megaloblasts being observed in a count of 100 leukocytes. By correcting for these, the total count of white blood cells becomes 19,800. In the stained film, the red cells showed considerable anisocytosis and poikilocytosis. One polychromatophilic megaloblast in mitosis was seen. The lymphocytes and mononuclear leukocytes, together, made up 53 per cent of the white blood cells or 10,500 per c.mm. of blood. The opinion, therefore, tended toward a diagnosis of lymphatic leukemia, possibly initiated by some underlying septic condition.

On June 27, blood examination showed 32,800 nucleated cells per c.mm. of blood. More than half of these were erythroblasts, 125 nucleated red cells to 100 leukocytes in the stained film. The corrected leukocyte count was, therefore, 14,600 per c.mm., of which 53 per cent were lymphocytes and mononuclear leukocytes. The abundant nucleated red cells in the stained film showed very little polychromasia. In nearly all of them, the cytoplasm stained* a salmon pink color, so that they could be easily distinguished from the lymphocytes, in which the faintly reticulated cytoplasm was stained blue.

The patient was given iron citrate by hypodermic injection, beginning on June 28, and $\frac{1}{4}$ grain of thyroid extract with the six-o'clock feeding. On July 2, Fowler's solution was given, 1 minim twice a day and later three times a day. On July 2, the patient was discharged with very little improvement. On July 18 he was brought to the Clinic. Orange juice was added to the feedings and the previous medication continued. It has since been learned that shortly after this last visit to the Clinic the patient died, but no autopsy was obtained.

CASE II.—S. M., male, aged five and a half months, was admitted August 28, 1922. The family history was negative. The patient was born at term, weighing 12 pounds. He had been exclusively breast fed. Since the age of six weeks he had appeared pale, according to the mother, and the skin had shown a progressively increasing yellow tint. Vomiting had been frequent. Upon admission to the hospital, the infant appeared fairly well developed and well nourished, without gross evidence of deformity. The skin was pale lemon color, the conjunctivæ, lips and buccal mucous membrane pale. The thorax appeared normal and without signs of rickets. The abdomen was distended and in it the enlarged spleen was very evident, extending below the iliac crest. The lower edge of the liver could be felt three finger breadths below the costal margin. The cervical, axillary and inguinal lymph nodes were enlarged.

Blood examination on August 28 showed only 3 gm. hemoglobin per 100 cc. of blood and red cells 2,084,000 per c.mm. The leukocytes numbered 50,000 per c.mm. (corrected count) and of these the lymphocytes and mononuclear leukocytes made up 73 per cent, or 36,500. In the differential count of 100 leukocytes, 92 nucleated red cells were seen (see Table II). On September 2, a transfusion of 120 cc. was given and on September 27 a second transfusion amounting to 140 cc. of blood. On the next day, September 28, the red cells were 4,179,000 per c.mm. and erythroblasts were not found in the stained film. The child was also given citrate of iron and Fowler's solution. On October 24, he was discharged, generally improved. On this day his blood examination showed 3,916,000 red cells, 9.2 gm. hemoglobin per 100 cc. and 9600 leukocytes per c.mm., of which 73 per cent were lymphocytes and mononuclear leukocytes. In the count of 100 leukocytes, 3 nucleated red cells, all normoblasts, were seen. On November 23 the patient died, the cause of death being given as anemia infantum.

* The tetrachrome blood stain was used.

TABLE II.—BLOOD PICTURE OF CASE II.

	Aug. 28	Sept. 2	Sept. 7	Sept. 27	Sept. 28	Oct. 10	Oct. 16	Oct. 24
Red cells	2,084,000	Trans- fusion	3,632,000	Trans- fusion	4,179,000	3,808,000	3,181,000	3,916,000
White cells	50,000		18,800		27,000	10,200	13,200	9,600
Hemoglobin (gm. per 100 cc.) .	3.0	with 120 cc. blood	7.6	with 140 cc. blood	8.9	9.6	7.0	9.2
Differential count (per cent)								
Polynuclears	22		24		18	18	31	20
Small lymphocytes	44		51		62	63	34	48
Large lymphocytes	28		19		20	14	22	19
Mononuclears	1		3		..	5	5	6
Transitionals	1		5	5
Eosinophils	4		2
Basophils
Myeloblasts
Disintegrated cells
Nucleated red cells (per 100 whites)								
Normoblasts	36		19		3
Microblasts	49		14	
Macroblasts	7		1	
Megaloblasts

CASE III.—N. I., aged six months, was admitted to the hospital on December 1, 1922. The family history was negative. The baby had been born at term with easy normal labor. He was breast fed for three months. On account of vomiting and loss of weight, he was then brought to the Clinic. Supplementary feeding with Dryco milk powder was given. Nearly three months later he was again brought to the Clinic, on account of fever and coughing. At this time an examination of the blood (on November 29) showed 1,808,000 red cells per c.mm., 3.9 gm. hemoglobin per 100 cc. and 23,000 white cells per c.mm. The patient was admitted to the hospital on December 1. At that time he was described as a dusky, anemic, undernourished and underdeveloped infant of six months, with open anterior fontanelle but without cranial deformity. There were no teeth. Lymph nodes were not palpable. Slight costochondral beading was recognized. Moist râles were heard at the base of either lung. The abdomen was distended, without rigidity or tenderness. The enlarged spleen extended nearly to the median line and almost to the pelvic brim. The liver extended 2 inches below the costal margin.

On December 4, an examination of the blood showed 1,648,000 red cells per c.mm. and 2.9 gm. hemoglobin per 100 cc. The count of nucleated cells was 23,400 per c.mm. The differential count showed 61 nucleated red cells (28 normoblasts, 25 microblasts, 7 macroblasts and 1 megaloblast) to 100 leukocytes. The corrected leukocyte count, therefore, became $14,500 \times \frac{100}{210} = 6,905$ of which 46 per cent were lymphocytes. The red cells showed marked poikilocytosis and anisocytosis and slight polychromatophilia and granular degeneration. Two macroblasts and one megaloblast were found in mitosis. A transfusion of 180 cc. was given on December 7, and on December 8 the red cells numbered 4,224,000 per c.mm. and the hemoglobin amounted to 10.4 gm. per 100 cc. The nucleated cells numbered 35,400 per c.mm. The differential count showed 110 nucleated red cells (69 normoblasts, 26 microblasts and 15 macroblasts) to 100 leukocytes. Hence the corrected numerical count of the leukocytes became $16,850 \times \frac{100}{210} = 7,995$. Ten days later the leukocytes had decreased to 8200 per c.mm. and nucleated red cells were not to be found.

In January the patient developed a purulent otitis media, first on the right side and then on the left. The anemia grew more severe, so that on

March 9 the red cells had fallen to 846,000 per c.mm. and the hemoglobin to 1.8 gm. per 100 cc. A transfusion of 200 cc. on March 12 was followed by an immediate improvement in the blood and a gradual healing of the ear condition. On April 6 a foul mucous shred was returned from each ear at irrigation and subsequently the irrigating fluid came away clear. On April 27 the patient was discharged, generally improved. The patient was afterward brought to the Clinic for four successive visits from May 14 to May 28, showing some improvement in appetite and in general symptoms, but after the last visit, his condition grew worse and about fifteen days later he died.

TABLE III.—BLOOD PICTURE OF CASE III.

	Nov. 29	Dec. 4	Dec. 7	Dec. 8	Dec. 18	Jan. 2	Feb. 5	Feb. 12	Mar. 9	Mar. 12	Mar. 13	Apr. 9
Red cells (millions per c.mm.)	1.8	1.6	Trans-11.2	4.4	4.1	2.1	2.4	0.8	Trans-4	3.7		
White cells (thousands per c.mm.)	23	14.5	fusion 6.8	8.2	11	11.4	7.4	10.6	fusion 6.2	7		
Hemoglobin (gm. per 100 cc.)	3.9	2.9	180 cc. 10.4	9.1	7.6	5.8	5.8	1.8	200 cc. 11.5	7.1		
Differential count (per cent)			of blood.						of blood			
Polynuclears	39	48		42	40	55	54	30		60	45	
Small lymphocytes	57	29		35	36	2	23	24	13	17	27	
Large lymphocytes	3	17		14	20	15	11	23	10	8	16	
Mononuclears	..	1		1	1	14	7	14	3	6	7	
Transitionals	..	3		4	2	8	1	4	3	2	5	
Eosinophils	1	1		1	..	5	3	3	1	4	..	
Basophils	..	1		3	1	1	1	2	..	3	..	
Myeloblasts	3	
Disintegrated cells	13	
Nucleated red cells (per 100 whites)												
Normoblasts	..	28		69	..	1	1	..	2	5	..	
Microblasts	..	25		26	1	1	1	5	..	
Macroblasts	..	7		15	..	1	2	2	..	
Megaloblasts	..	1		

Discussion. These three patients are examples of a rather peculiar anemia of young children, the most striking feature of which is the unusually large number of nucleated red cells in the circulating blood, at times outnumbering the leukocytes. The blood picture thus resembles von Jaksch's disease, though the uniformly relatively rapid fatal outcome, differing from the majority of such cases, suggests that they may represent a more definite subgroup. In addition, there is usually an evident enlargement of the spleen, sometimes of the liver also, and a marked relative and absolute increase of the lymphocytes in the circulating blood. The features of the disorder appear to be sufficiently distinct and definite to justify its recognition as a disease entity.

The etiology is obscure. There appears not to be a familial factor, nor is there any suggestion of tuberculosis or syphilis in the etiology. The children in this series were born at full term, which would appear to exclude prematurity as a factor. There is possibly a suggestion that a disordered digestive function may be the underlying cause of this sort of anemia and the marked increase of lymphocytes in the circulating blood might be regarded as a result of gastrointestinal irritation. Recent research^{6, 7} upon intestinal bacteria in relation to anemia suggests that studies of intestinal bacteriology might help to elucidate this disease.

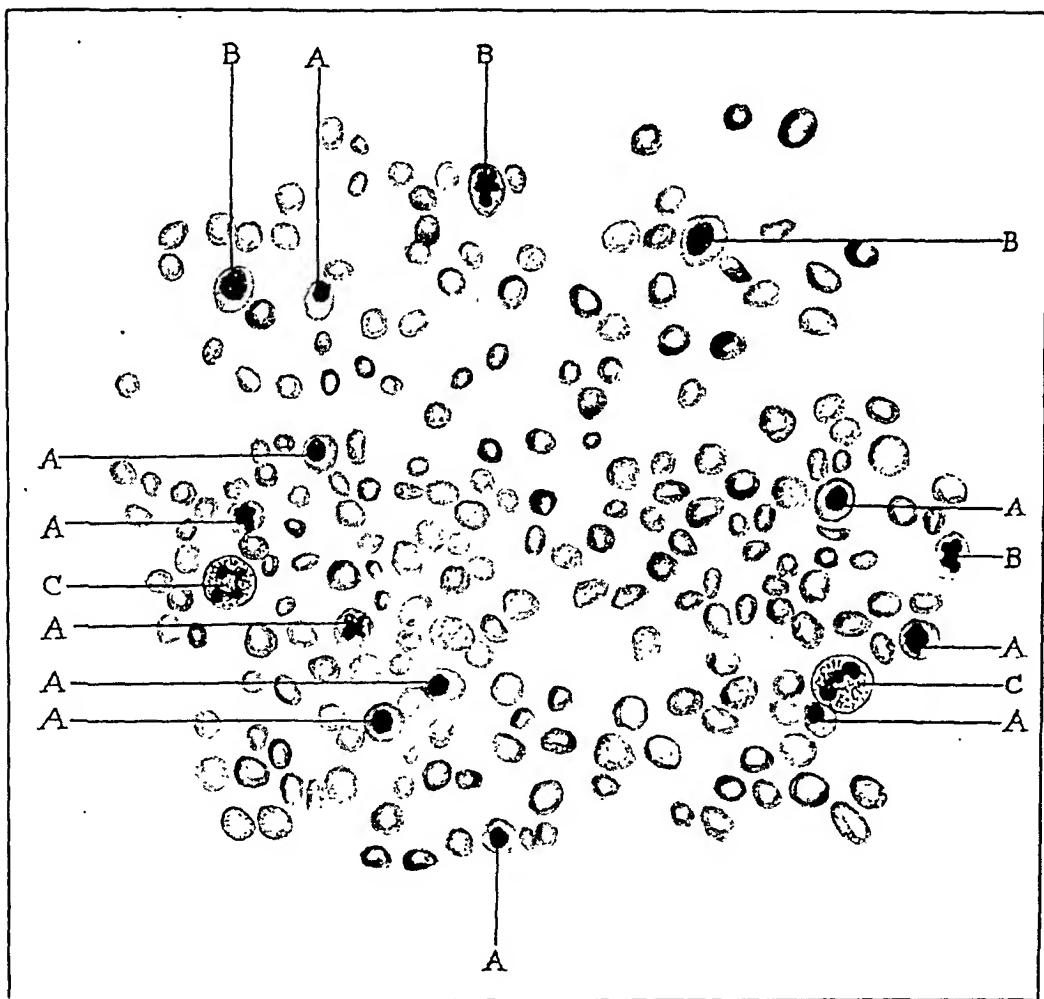


FIG. 1.—Portion of smear for differential count taken from Case I on June 27. *A*, normoblasts; *B*, macroblasts; *C*, polymorphonuclear neutrophil leukocytes.

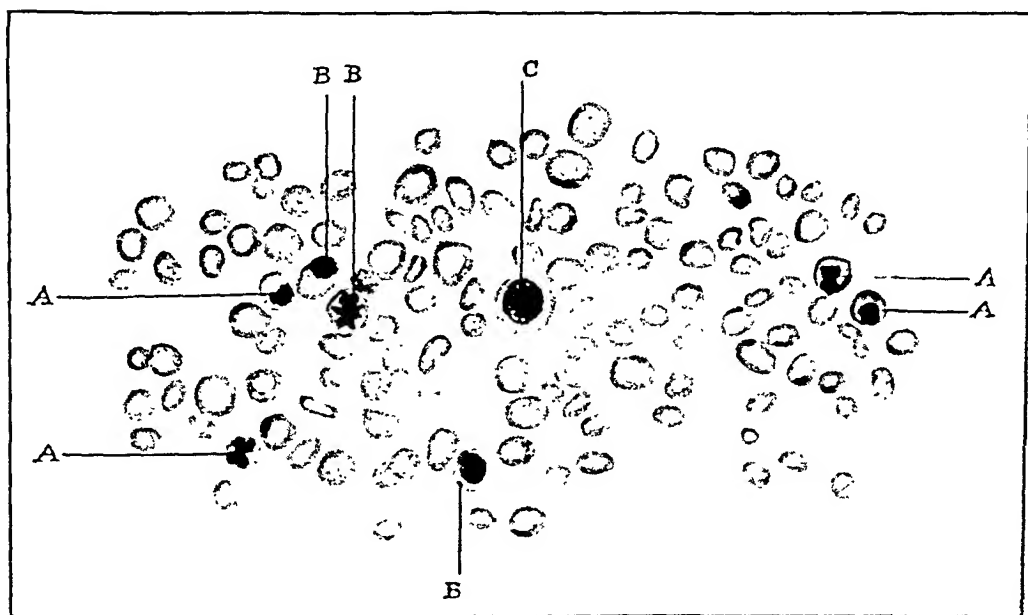
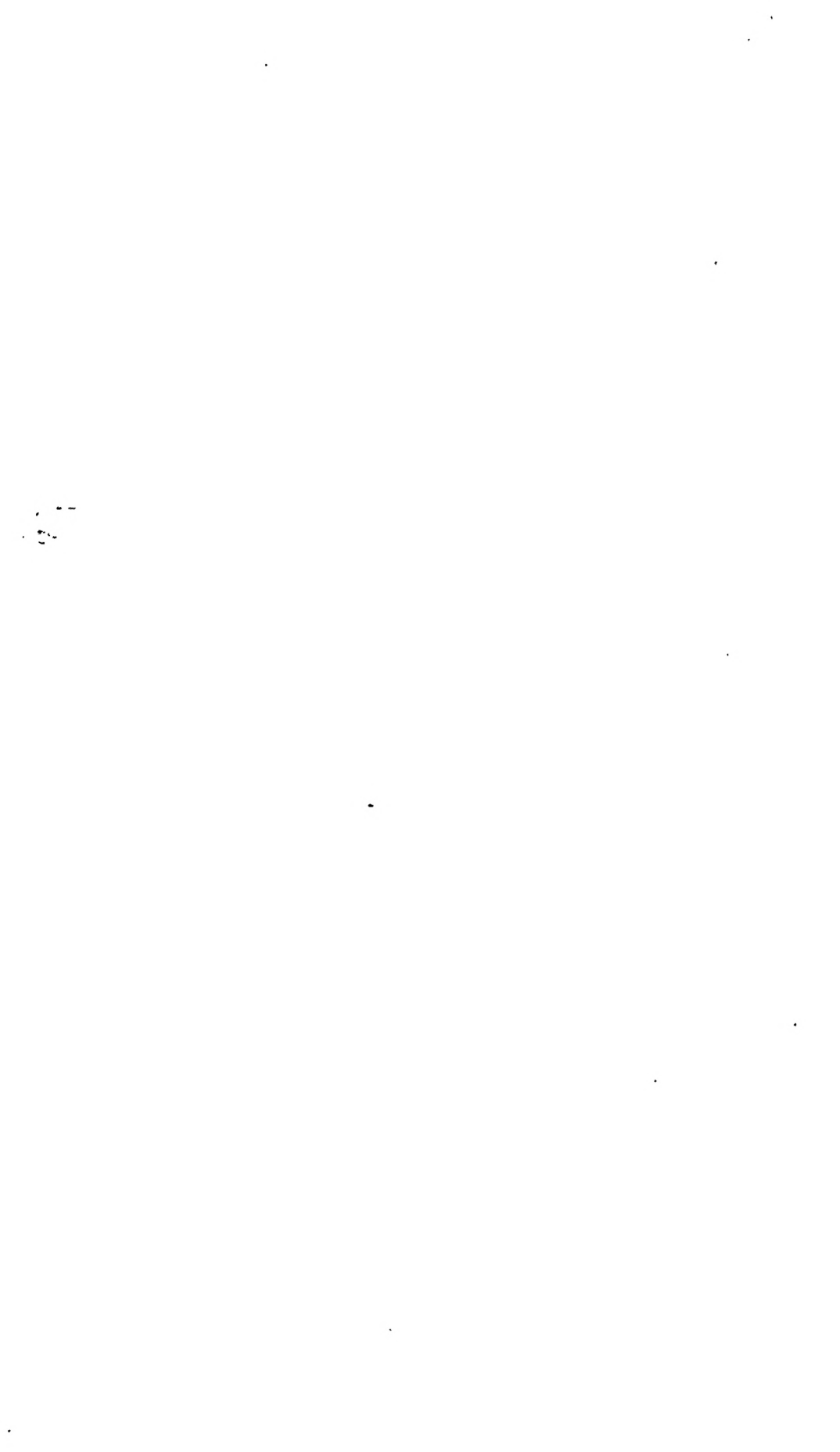


FIG. 2.—Another field from the same smear. *A*, normoblasts; *B*, macroblasts; *C*, megaloblast.



On the basis of the clinical features and the anatomic changes in the blood, even without an understanding of the etiology, it seems wise still to regard this disorder as a disease entity. The suggestion of Cooley that it be designated as erythroblastic anemia or erythroblastemia appears excellent, as it places emphasis upon the most strikingly peculiar anatomic feature of the disorder. However, the name of von Jaksch will doubtless continue to be employed in the designation of this and other anemias in children with a similar blood picture for some time to come.

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PAIN OF CENTRAL ORIGIN.

A DISCUSSION OF SOME DISEASES OF THE CENTRAL NERVOUS SYSTEM IN WHICH PAIN IS A MAIN SYMPTOM*

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ALL progress in our understanding and knowledge of the human body has been from the periphery to the interior; parts readily reached in exploration yield many of their secrets long before the deeper lying structures. It was known for untold ages that irritation of a sensory nerve was productive of pain. Later it was discovered that the dorsal nerve roots possessed the same function, but only in recent years has it been appreciated that the deeper-lying spinal cord and brain (that is, central nervous system) will respond by

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painful sensations to noxious stimuli. In the same sense, it has long been understood that diseases of the peripheral nerves and their roots usually are painful whereas morbid processes centered in the brain and cord are not often attended with suffering. Although the latter statement is true in a general way, there are enough instances of pain central in origin to make the phenomenon by no means a rarity.

Many workers have contributed their share in demonstrating the existence of pain of central origin as well as of the diseases with which it is associated, and there are many theories concerning the mechanism involved in its production. The literature on the subject is already voluminous and it is beyond the scope of this article to enter into all the theoretic considerations of the causation of the phenomenon and its relation to the functions of sensation as a whole. The attempt here will be to discuss the more common clinical conditions associated with pain of central origin and corresponding with different levels of the central nervous system. It may be mentioned that pains not associated with obvious organic lesions, the various types of so-called psychalgia or pains of hysterical, neurasthenic and altogether psychoneurotic origin, have considerable interest in themselves but do not lend themselves to the elucidation of a problem such as this. Only instances were studied wherein the pain was produced by a definite structural alteration of the central nervous system, whatever the cause.

In order to start with simpler structures and to pass to those more complex, the levels of origin of central pain are followed up the pathways of incoming sensory impulses, through the spinal cord and brain stem, into the cerebrum, and finally to their destination in the cortex.

Lesions of the Spinal Cord. Among the many different lesions involving the spinal cord, it is difficult to understand why so seldom pain is produced that may be considered of central origin and quite apart from that due to involvement of the dorsal roots. In an article regarding traumatic lesions, Holmes described a group of patients who, during the World War, received gunshot injuries affecting the spinal cord indirectly. The majority of these patients had wounds in the neck near the cervical portion of the spinal cord and which usually affected one side of it by concussion, so that a Brown-Séquard syndrome resulted. Almost immediately following the injury there appeared below the level of the lesion burning, shooting, stabbing pain that was more marked in the lower extremity that had become paralyzed but that remained normally sensitive. This was poorly described and poorly localized by the patient. It was increased by peripheral stimuli, particularly by passive movement of the leg or even by jarring of the bed, and it was seldom severe or persistent in the side that was anesthetic to pain, touch or temperature. Pin prick and thermal stimuli were extremely

unpleasant and resulting responses tended to radiate widely over the limb, although the thresholds for pain and thermal stimuli were unaltered or even slightly raised. The pain reached its maximum in about two or three days and then gradually disappeared in about three weeks. Holmes considered the pain in the limbs to be due to a lesion of the cord that, although injuring and irritating the fibers carrying impulses of pain, did not destroy them. Possibly the spinothalamic tracts were concerned in this pain but since vibration stimuli produced painful and unpleasant sensations, Holmes considered that the dorsal columns were at least partly responsible. Foerster has observed similar cases and mentioned one case in which, following injury to the cord, an imperfect Brown-Séquard syndrome resulted. Right-sided spastic paralysis of the leg and left-sided thermesthesia were present, but disturbance in perception of pain was not observed; the patient complained of a persistent severe pain in the left leg. In more severe direct lesions to the cord, hematomyelia may result and at the time of its formation, especially in the cervical part of the cord, this may produce pain in the lower extremities.

Syringomyelia in the majority of cases runs a completely painless course to its end; the painlessness of burns, cuts and bruises in anesthetic areas is a classical feature of the disease. Yet cases of syringomyelia have been reported wherein pain was persistent throughout the course of the disease. Oppenheim remarked that pain is not uncommon, and Raymond and L'hermitte described a spinal form of syringomyelia characterized by intense pain. Schlesinger, Haenel, Dejerine and Thomas, and Taylor, Greenfield and Martin also described cases wherein pain was a prominent symptom. Harris, in a recent article, mentioned that pains in the back and limbs may sometimes precede for years any sensory or motor symptoms in this condition and stated: "The possibility of such aching, boring, burning neuralgias being due to this form of chronic spinal disease is perhaps hardly sufficiently insisted on."

Earlier authors ascribed the origin of the pain in syringomyelia to involvement of the dorsal roots by associated meningitis. Later it was admitted that it might occur from irritation of the intramedullary pain tracts and thereby produce pain remote from the site of the lesion or that it might even be segmental in distribution and due to the syringomyelic cleft involving the dorsal horns of gray matter in the cord. Spiller²⁵ recently supported the latter hypothesis by the publication of the case of a patient he had examined, including details learned at necropsy. The patient had complained of spontaneous, dull, aching pains in both lower extremities. Examination of the cord, however, showed that the syringomyelic cleft had not reached the lumbar region and that the roots supplying the lower extremities with their meninges were entirely normal. It was, therefore, a reasonable conclusion that the pain was due to

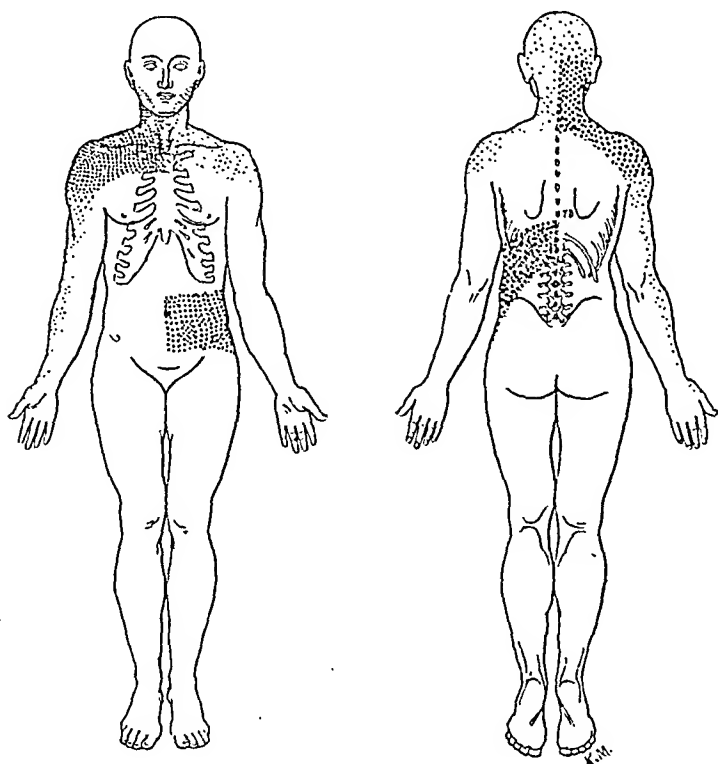
involvement of the spinothalamic tracts above the segmental area supplying the lower extremities. In such cases of syringomyelia the distribution of pain may be bilateral, as in the case of Spiller, or down one complete side of the body. More frequently, however, the pain is segmentally distributed as in the following illustrative case.

Case Reports. CASE I.—An unmarried woman, aged twenty-two years, came to the Mayo Clinic, June 15, 1926, complaining of pain in the neck and back. She never had been very robust, and at the age of eleven years severe, sharp pain developed over the left side of the neck, extending down the posterior aspect of the arm and settling in the left wrist. She had had these attacks of pain over a period of six or seven months when they had gradually diminished, leaving occasional dull, aching pains throughout the posterior aspect of both arms and extending to the wrists. Since this first attack of pain, the left hand had been somewhat weaker, deeper red and perspired more easily. Four years before sharp, shooting pains had developed which had radiated from the right side of the neck and mastoid region up toward the vertex. These pains had been associated with a feeling of stiffness in the muscles of the neck, and they disturbed her sleep at night. Attacks of these pains would last from two to four days, with relief for another few days and then would appear again. About the same time as the pain in the neck and head had appeared she had begun to suffer from a similar type of pain in the left lumbar region. This would radiate from about the region of the third lumbar vertebra, laterally around the trunk toward the anterior-superior spine of the ilium. This pain had been of the same sharp, shooting character, and during one period had been present daily for five weeks. The patient had thought that heat would relieve the pain in her back and, accordingly, she had used a hot-water bottle frequently on that area. At the same time she had noticed that the sensation of heat was not very well felt in the painful areas, and on one occasion at least she had fallen asleep on a hot-water bottle and had burned herself severely without being conscious that she was doing so. The periods of pain had become more and more frequent until, when she came to the clinic, they were usually constant, dull and aching in type, with exacerbations of sharp, shooting pain, especially on exposure to exertion and excitement.

On general examination, the most conspicuous feature on inspection was the peculiar appearance of the left hand. This was soft, atonic, red, flabby, sweating and atrophic, and there was a much greater number of creases on the palm than on that of the other hand. There was definite weakness of the muscles of the hand; the atrophy was mainly in the interossei, opponens pollicis and hypothenar muscles. The grip was weak and the tendon reflexes were absent on the affected side. Also, on the right side, the biceps reflex was lost, but the triceps and supinator reflexes were still active. Hoffmann's sign was present on this side. The patellar and Achilles' reflexes were exaggerated. The plantar reflexes were flexor in type, and the abdominal reflexes were absent on the right side. Horizontal nystagmus when the patient looked to the right, and unsustained vertical nystagmus were present. Over the back, about the region of the eighth to the twelfth thoracic segments on the left side, there was the scar of a healed burn. There was marked diminution of sensation, especially for pain and temperature, in a capelike distribution over the neck and shoulders, in or about the region of the second, third, fourth and fifth cervical segments; tactile sensibility was normal. In the region of the lumbar pain, that is, in the segments supplied by the eighth to the twelfth dorsal

roots on the left side, there was an area of hyperesthesia to temperature and pain which included the area of the burn (Fig. 1). In neither of the areas mentioned was there complete anesthesia for painful stimuli, but a marked diminution in ability to feel pin pricks. Moderate scoliosis in the dorsolumbar spine was observed.

A diagnosis of syringomyelia was made and treatment with Roentgen rays was given over the cervical and thoracic portions of the spine. The patient was requested to return for further treatment, but did not do so. When last heard of, February 15, 1929, she was apparently still suffering, but information could not be obtained as to the exact status.



MAYO CLINIC

FIG. 1.—Sensory chart in the case of a patient with syringomyelia accompanied by severe pain. The stippled areas represent diminution to pain and thermal sensibility. Anesthesia was not complete.

Similarly to syringomyelia, it is possible for hydromyelia to cause pains by compression of the spinothalamic tracts and posterior columns of gray matter in the cord. Foerster reported the case of a patient whom he had operated upon for intramedullary tumor. There were pains in the fifth thoracic segmental area, paralysis of the legs, incontinence of urine and hypesthesia for all kinds of sensation from the sixth thoracic to the third sacral segments. The patient also complained of severe pain in both lower extremities. At operation a hydromyelic cyst was found at the sixth thoracic segment. It was opened and there was prompt relief of all pain. The paralysis improved also but gradually it returned.

Both intramedullary and extramedullary tumors which involve

the spinal cord sometimes produce pains that are not segmentally distributed and due to compression of the roots but that are situated in regions well below the site of the lesions. Considering how frequently the spinothalamic tracts are involved by compression in cases of tumor, it is surprising that this does not occur more frequently. Elsberg mentioned having a number of cases in his series of tumors of the spinal cord wherein the first symptom complained of was pain in a part of the body distant from the region supplied by the nerve roots at the level of the tumor. This is relatively more common in tumors of the cervical and upper thoracic regions. Often the pain is felt in a lower extremity, on the side opposite to that of the tumor; it may come on early in the course of the compression of the cord by the tumor and before root pains appear. Also, root pains may never appear and these distant pains may constitute a prominent symptom. These manifestations are very confusing and might suggest that the tumor was situated low in the lumbar or sacral part of the spinal canal, when, as is later demonstrated, the pain was due to irritation of the spinothalamic tracts high in the cervical region and on the opposite side. Also, it is not uncommon to find patients, who have had tumors of the spinal cord removed, suffering from constant, severe, burning pains in the lower extremities; the pains appear coincident with the lessening of the anesthesia and during convalescence from operation. Later, with the restitution of both motor and sensory function, these pains disappear.

CASE II.—A woman, aged fifty-one years, was brought to the Mayo Clinic, November 3, 1926, because of paralysis of the lower extremities. Eleven months previously she had noticed twitching and quivering of the muscles of the calves of the legs; this condition persisted intermittently throughout the winter. Six months before admission she had noticed that on walking her limbs were not clearing the floor and that there was a tendency to hit against obstacles in her path; this was somewhat worse on the right side. This weakness, clumsiness and stiffness of the lower extremities had persisted, gradually getting worse, and finally reaching the stage of complete paralysis two months before admission to the Clinic. Five months before, and for a period of two or three months, she had suffered intense pains in both lower extremities, chiefly in the posterior aspect of the limb. The pain had extended as high as the hips. This pain had been felt deep in the leg, had disturbed her sleep at night and had not responded to any of the ordinary methods of treatment. Gradually, however, with the onset of numbness and loss of sensation of both lower extremities, this pain had disappeared. The numbness had increased and reached a level about the region of the umbilicus. Incontinence of urine had appeared about twelve days before examination.

Examination disclosed complete paralysis of both lower extremities, of the muscles of the lower part of the back and of the abdominal muscles. There was anesthesia for pain, tactile and thermal sensibility as high as the ninth thoracic segment on the left and the tenth thoracic segment on the right. Tendon reflexes were exaggerated in the lower extremities, and Babinski's sign was present bilaterally. A positive Queckenstedt test was revealed after spinal puncture.

The patient was operated upon, November 11, 1926 (Adson), and a subdural, extramedullary meningioma was found opposite the sixth and seventh thoracic vertebræ, on the right dorsolateral aspect of the cord. The tumor was oval, about 15 mm. long and 12 mm. in diameter. The cord was compressed to about two-thirds of its normal size.

After a somewhat prolonged convalescence the patient made a good recovery.

Experimentally pain may be produced by irritation of the structures within the spinal cord. Dusser de Barenne injected strychnin into the posterior horns in animals and produced severe pain in the corresponding segmental cutaneous zones. By pricking, by cutting and even by touching the anterolateral funiculi, Foerster has produced pain on the opposite side of the body. Once, while injecting a dorsal root with procain, his needle penetrated the dura and stabbed the cord, producing terrific pain in the opposite lower extremity.

Lesions of the Medulla Oblongata. The spinothalamic tracts are continued up into the medulla and, lying dorsolateral to the inferior olivary nucleus, they come in close relationship with the spinal root of the fifth nerve and its nucleus. A single lesion in this region may involve both these structures and may produce anesthesia for pain and temperature on the side of the lesion in the area supplied by the fifth nerve as well as in the opposite side of the body. One good example of such a lesion is the area of softening produced by thrombosis of the posterior inferior cerebellar artery. The whole clinical syndrome produced by this lesion is sufficiently well known not to need further description beyond mention of this crossed anesthesia for pain and temperature that is so characteristic. One of the best reviews written in the past was by Spiller, and more recently Bergmark again has told all that is known about it. It is not generally known that pain may occur in one or more of the anesthetic areas. Among cases described with necropsy, in Wallenberg's case pain was present first in the eye, and later in the entire side of the face on the side of the lesion; this also was present in one of the two cases described by Thomas. In the case reported by Hun, at one time in the course of the disease the patient had pain in the face on the affected side. Among the clinical cases described, Hall mentioned that he had seen a patient who had suffered from occlusion of the posterior inferior cerebellar artery and who complained of considerable pain, which was more or less paroxysmal, on the affected side. In Gowler and Hope's case there was intense burning, tingling, persistent pain over the whole left side of the body and on both sides of the face. Case III presents a similar situation.

CASE III.—A man, aged fifty-two years, came to the Mayo Clinic, May 19, 1923, because of pain in the left side of the face and unsteadiness in gait. Seven months before, following a period of great activity in his business, he had a sudden attack of vertigo while at lunch. This vertigo had persisted, and within a few minutes vomiting of a forceful and persistent type

had come on, had continued for several hours and, finally, had been relieved by opiates. The patient had wakened the next morning to find that he had complete paralysis of the muscles of swallowing and his voice was very hoarse. The dysphagia had improved somewhat within forty-eight hours, but thereafter hiccough had come on which had been very distressing and which had lasted four days. The examining physician had noticed at this time some diminution of sensibility to pain over the neck, limbs and trunk on the right side and over the face on the left side. The patient himself had noticed that he had burned the fingers of the right hand with a cigarette and did not feel the burn; there also had been a painless traumatic ulcer in the left nostril as the result of his picking it with his finger nail. After five days in bed, during which time improvement was continuous, the patient had left his bed and had found that he was very unsteady on his feet, with a tendency to stagger to the left; he also had noticed that he had incoördination in the motions of his left arm on attempting to dress himself. The dysphagia had continued to a lesser degree and the hoarseness likewise had persisted.

Three months after the onset, pain gradually had appeared in the face, chiefly in the left temporal fossa, but later spreading over the major portion of the region supplied by the fifth nerve. At first this pain had been intermittent and mild; later it had become constant and intensely severe, representing one of the most prominent features of the trouble. The patient had had considerable difficulty at night from choking and gagging, due no doubt to the pharyngeal paralysis, and, frequently, he would waken coughing and spluttering, at which time the pain in his face would become very intense. Up to the time of examination at the Clinic the pain had been so severe that the patient had needed a considerable quantity of opiates for relief. External stimuli seemed not to have any influence on the severity of the pain. It came and went, irrespective of whatever he might be doing. It was most severe in the left temporal fossa and around the left orbit. An adequate description of its character could not be given by the patient.

On examination, the patient was seen to be a haggard, round-shouldered man, with a somewhat large head, and apparently in very acute pain. Nevertheless his expression was dull and drowsy and his attention was obviously impaired, possibly due to opiates administered for relief of pain. During examination he complained of constant discomfort or pain in the left side of the face; on this pain were superimposed, about every ten minutes, severe paroxysms which made him contort the left side of the face and produced flushing and lacrimation. Horizontal nystagmus and vertical nystagmus, which was well sustained, were present. The left side of the pharynx was paralyzed, as was the vocal cord on that side. There was complete anesthesia to painful and thermal stimuli, as far as could be judged, over the area of distribution of the left fifth cranial nerve, with abolition of the corneal reflex on that side. There was similar but less marked loss of response to painful and thermal stimuli over the right side of the trunk and neck, and in the right arm and leg. Minor degrees of sensibility could not be estimated because of the patient's mental state. Tactile sensibility was everywhere apparently normal, but vibration sensibility was diminished in the limbs on the left side of the body. There was a slight degree of incoördination in the left arm and leg and the gait was moderately ataxic, with a tendency to lurch to the left. Observation of this case was, of necessity, somewhat limited and occupied only a few days. The patient left the Clinic and was not seen again. A letter from his wife stated that, although the pain had somewhat diminished, he died suddenly three months after his departure. The cause of death, as given by the local physician, was a stroke of apoplexy. It was reasonable to assume from our previous study of the patient that he had had another thrombus in the same system of bloodvessels, but extending this time more widely.

It is not only in cases of syringomyelia of the spinal cord that pain may appear but also in cases wherein the same disease attacks the medulla. In the case recorded by Foix, Thevenard and Nicolesco, the patient had at the outset continuous burning pain in the right side of the neck. Later it spread to the face and head. There were also crises of agonizing pain lasting five to ten minutes, mainly spontaneous but frequently initiated by touching or washing the face, stroking the beard, and by currents of cold air. Later the same pain and anesthesia appeared in the opposite side of the face but to a much less degree. Treatment by injections of alcohol into the nerve were of no avail and finally the patient died of an inter-current affection. At necropsy a syringomyelic cleft was found involving the spinal roots and nucleus of the fifth nerve on the right. It extended from the upper part of this nucleus down to the fifth or sixth cervical segment of the cord and occupied mainly the nucleus of the fifth cranial nerve and the corresponding substantia gelatinosa of the cord. On the left side, in the nucleus of the fifth nerve there was the beginning of gliosis without cavitation.

Foerster had a similar experience with a patient who had a severe trigeminal neuralgic pain at the onset of syringobulbia and before diagnosis was possible. He, however, went further for the relief of this pain and after trying alcoholic injection of the Gasserian ganglion, cut the posterior root of the fifth nerve, without any effect whatever on the pain. Typical signs of syringobulbia ultimately developed and progressed caudad. Pain in the pharynx, ear, occiput and neck appeared in the order given; the pains first appeared in areas of normal sensibility but gradually, as sensation for pain disappeared, the pain diminished.

The visceral afferent component of the vagus, according to Ranson terminates in the nucleus of the tractus solitarius. Its situation just under the floor of the fourth ventricle renders it subject to irritation by tumors occupying this cavity. Nevertheless, although an early and fairly constant symptom of these tumors is vomiting, due in all probability to irritation of the dorsal nucleus of the vagus and its visceral efferent fibers, subjective sensations indicating disturbance of the visceral afferent component are rare. However, Sachs reported the case of a man suffering from a papilloma of the choroid plexus of the fourth ventricle, in whom, as well as the usual vomiting, there was complaint of abdominal pain. At operation, the patient, who had had a local anesthetic, suffered this same pain during the manipulations of the tumor prior to its successful removal. Symptoms of pain also ceased thereafter. I have observed two similar cases of patients with tumors involving the fourth ventricle and wherein the early vomiting so characteristic of the lesion was associated with abdominal pain, poorly localized and poorly described by the patient. Since vomiting and abdominal pain may occur long before increased intracranial pressure has been disclosed

by papilledema and headaches, the vomiting and abdominal pain may be attributed to a condition other than an intracranial disorder, and the result may be a diagnostic error. In the two cases mentioned, examination at necropsy did not show other cause of abdominal pain.

Lesions of the Pons. Just as in the medulla, various lesions situated in the pons may give rise to pain by involvement of the fifth cranial nerve and the ascending spinothalamic tracts. At least two cases of tuberculoma of the pons are recorded with central pain. Economo's patient had pain severe enough to require opiates for relief. The pain was felt in the right side of the body, in the arm, leg, chest and abdomen. Pain was not present in areas supplied either by the left or right fifth cranial nerves. Among other numerous signs of pontine involvement there was also crossed anesthesia for pain and thermal sensibility affecting the left side of the face and the whole right side of the body. Sensibility to touch was everywhere intact. The lesion proved to be a tuberculoma, chiefly on the left side of the pons, and its greatest width was at the region of the main sensory nucleus of the fifth cranial nerve so that both motor and sensory portions of the fifth cranial nerve were severely affected.

The patient of Weisenburg and Stack also had a tuberculoma of the pons and it likewise was unilateral but occupied the right side. It reached its maximal size in the lower part of the pons. Six months after onset of signs of the disease the patient complained of pain in the entire left side of the body, at first intermittent, and later constant. The pain was described as "burning, grinding, disagreeable and unbearable." Later, pain appeared in the right side of the face and there was hyperesthesia to pin pricks in that area. Sensitivity to heat and cold were only slightly diminished on the right side of the face but tactile sensation was almost lost. On the left side of the body, thermal and tactile sensibility were greatly diminished and these stimuli produced marked paresthesia and exaggerated affective reactions.

Herpes involving the fifth cranial nerve, especially in its first and second divisions, is often associated with persistent, severe, constant, burning pain, unpleasant paresthesia and hypersensitivity in the region involved. Particularly in elderly persons, these symptoms may persist for many years after the acute phase has passed. Often the scars which are left are anesthetic or anesthesia may be spread over wider areas and at any time in the course of this so-called postherpetic neuralgia around the forehead, orbit and cheek there may be a strange medley of pain, hyperesthesia and anesthesia.

Injection of alcohol into the nerve or its ganglion, avulsion of the supraorbital nerve and even section of the posterior root of the Gasserian ganglion or avulsion of the ganglion has been done for relief of pain without, however, any constant success. The follow-

ing example represents one in which avulsion of the ganglion failed to relieve the patient's complaint.

CASE IV.—A man, aged fifty-six years, came to The Mayo Clinic, July 14, 1921, complaining of pain in the left orbit and left temporal region. Ten months before, while sitting in the open air, he had noticed some pain and soreness in the left eye. Immediately the eye had become red and swollen and within twenty-four hours this redness and swelling had extended over the left side of the forehead, temporal region and cheek. Accompanying this there had been agonizing pain in the forehead and orbit and for many days he had been delirious with pain and had been under opiates constantly. When pain had somewhat subsided and he was able to observe his condition, he had noticed ulcers over the forehead, cheek and temporal region, and the eye was badly injured. He also had noticed that along with the severe pain there was a certain degree of numbness over the areas of ulceration. Seven months from the time of onset of the illness the left eye had to be removed, and the original pain, although not so intensely severe, had still persisted and was very distressing. At the time of examination, he complained of constant burning numbness in the orbit, temple, forehead and anterior portion of the scalp on the left side.



FIG. 2.—Herpes of the left fifth cranial nerve; extensive areas of scarring and loss of the eye are shown.

On examination, the patient was seen to be worn and emaciated, with obvious scarring left by previous herpes of the first and second divisions of the fifth cranial nerve (Fig. 2). The eye socket contained a stump left by previous operation and there was some purulent discharge from the socket. He had rather marked anesthesia for pain, and tactile and thermal sensibility over the forehead, orbit, temple and upper part of the left side of the bridge of the nose. Around the area of deeper anesthesia, over the

scalp, cheek and ala of the nose, were minor sensory changes. The anesthesia largely corresponded in degree and distribution to the extent of scarring. Hyperthesia was not present. The patient was somewhat senile in appearance and reactions, and a moderate degree of peripheral arteriosclerosis was present.

Operation was performed, July 23, 1921. The posterior root was completely cut and the ganglion was avulsed. Convalescence was satisfactory.

On reëxamination, about two weeks after the operation, the patient had complete anesthesia for all qualities of sensation in the area supplied by the left fifth cranial nerve, as well as paralysis of the muscles of mastication. He complained, however, that the pain was still present and, if anything, worse than before the operation. He stated that he felt the pain after operation, as before, in the region of the left temporal muscle, and that it was most severe deep in the socket of the left eye. There also was some pain over the vertex and jaw, where the areas supplied by the fifth cranial and the cervical nerves join. He has not been heard from since.

The persistence of pain in this case may have been due to a lesion in the trigeminal nucleus occurring at the time of the original herpetic attack and therefore refractory to section of the fifth nerve outside the pons. In herpes zoster, the lesions in severe cases are not confined to the spinal ganglions but invade the dorsal horns of gray matter in the cord; the same is probably true in the homologous Gasserian ganglion. Accordingly, residual effects of the inflammatory lesions of the pons and of the tissue around the sensory nuclei of the fifth cranial nerve may serve to perpetuate the patient's suffering.

Lesions of the Optic Thalamus. Although the plan followed so far has been to trace the possible sites of painful lesions up the cord and brain stem to the thalamus, historically at least this organ holds first rank as a source of central pain and other affective phenomena. For a considerable period it has been thought to be the only source. Spiller, in 1922, stated: "I should like to have evidence that a lesion entirely below the optic thalamus may cause spontaneous pain in one-half of the body." It was his privilege in 1923 to fill in this gap in knowledge, ably supported by Weisenburg and Stack. Recent writers, including Wilson, have agreed that spontaneous pains and various types of unpleasant sensations hitherto considered characteristic of lesions of the thalamus may arise as sequels to structural disease anywhere below the thalamic level. Although the so-called syndrome of the thalamus is no longer considered peculiar to thalamic lesions, yet the original work of Dejerine and Roussy is worth recalling; however their interpretation and that of Head may be doubted, it does not dim the luster of their original masterly description.

In 1906, following the observation of a series of 5 patients with focal thrombotic softening in the region of the thalamus, Dejerine and Roussy published a description of what they called the syndrome of the optic thalamus. They defined it as: (1) slight hemiplegia, usually without contracture, and disappearing rapidly; (2)

persistent hemianesthesia, organic in type, and always associated with marked and persistent loss of deep sensibility; (3) mild hemi-ataxia and astereognosis, the latter more or less complete; (4) sharp, persistent, paroxysmal pains felt in the hemiplegic side of the body, often intolerable and not yielding to treatment, and (5) choreo-athetotic movements in the limbs of the paralyzed side. They considered the first three as major features and the last two as being relatively less constant.

The onset of symptoms was sudden but with as little general shock as one would suppose with a small focus of thrombotic softening. Although the motor weakness rapidly diminished, the sensory signs persisted until death, which might not ensue for years. More in detail the sensory disturbance, objectively, consisted of diminution but never of loss of pain, temperature and tactile sensibility, while sensibility to vibration, muscle sense, the power of estimating the weight, size, shape and contour of objects were profoundly affected. Either at the onset of the disease or comparatively early, subjective discomfort appeared not only in the paralyzed limbs but also in the side of the face and trunk. Chiefly, these discomforts were in the form of pains that radiated along the whole length of the limbs affected; they were poorly localized and occasionally were described as being in the skin and subcutaneous tissues. They were constant, with, however, paroxysmal exacerbations severe enough to make the patient cry out and to impair sleep. Not only were the pains apparently spontaneous but they could be evoked by touching the skin, by pin pricks and by cold water. Deep pressure especially was intensely disagreeable. The patients described the pain in many ways and used adjectives such as burning, darting, squeezing and stabbing. Between the crises of pain there was complaint of formication and various types of paresthesia including a sensation of swelling in the limbs, trunk and face.

In the cases studied at necropsy the anatomic lesion found by Dejerine and Roussy was a small focus of softening, chiefly in the lateral nucleus of the thalamus, in its posterolateral part, although the median and internal nuclei and part of the internal capsule were affected to a lesser degree.

Since Dejerine and Roussy's work, contributions too numerous to mention have been published dealing with lesions of the thalamus. Among them is that of Holmes and Head, published in 1911. Later, this work was further elaborated from a study of 24 cases and described in great detail in Head's book, published in 1920. The description given by one of his patients, of her own pains, is worth quoting: "ever since this 'stroke' she has suffered from pains in the left half of the body, and an uncomfortable sensation as if something were crawling under her skin. These pains are intense in the hip, the loin and under the left shoulder. They are said 'to pump up and down the side' and the left arm and leg 'feel as if they

were bursting.' Whenever there was cause for visceral discomfort, such as the passage of a constipated motion, these pains became particularly severe, and the heart is said to 'throb' and the stomach to 'work' painfully, but on the left side only."

In Head's work emphasis is laid on the excessive response to affective stimuli. In all of his 24 cases the response to pin pricks, to extreme ranges of heat and cold and to pressure was intense. The threshold for the stimulus might actually be raised, but once the sensation reached consciousness it was responded to more profoundly than on the normal side. A patient might call a pin prick a touch when lightly applied but if the pressure were increased it finally would produce an intolerable sensation of discomfort. Not only were painful stimuli in Head's cases responded to with this overloading of feeling tone, but agreeable sensations, such as pleasant degrees of heat, were equally intensely felt and responded to with greater pleasure than that felt on the normal side. In these cases also, when a pin was dragged across the body from the normal to the affected side, an intense degree of discomfort was experienced once the median line was crossed.

An interesting feature of thalamic lesions was illustrated also by Head in the effect of emotion on these patients. Music was peculiarly likely to evoke a different reaction on the two halves of the body. One of the patients could not go to church because he "could not stand the hymns on his affected side." In another, during the funeral service for the late King Edward VII, as soon as the choir began to sing he felt "a horrid feeling come on in the affected side and the leg was screwed up and started to shake." In many of these patients, therefore, the mental emotions evoked by music or by disagreeable sounds intensified preëxisting pains and discomfort. Other lesions of the thalamus producing the so-called thalamic syndrome have been described, among which may be mentioned inflammations such as epidemic encephalitis, traumatic lesions and tumors.

CASE V.—A man, aged sixty years, came to the Mayo Clinic, August 13, 1928. He complained of residual weakness of the right side of the body and severe continuous pain over the whole left side. Five years before, while working as a fireman, he had come in contact with a current of 2300 volts and had been severely shocked. He immediately had become unconscious and had remained so for five hours. On regaining consciousness, it has been discovered that he had paralysis of the right side with aphasia and complete anesthesia on that side. He had very little memory as to what had occurred for the first three or four weeks of his illness, but at the end of that time movement had commenced to return on the right side and ultimately had returned to almost normal as far as motor function was concerned. The aphasia had disappeared also within a few weeks, but the right-sided anesthesia, although improved to a certain extent, had persisted and had remained more or less profound up to the time of examination. Pain had made its appearance within a few weeks from the time of the injury, about the time the motor and sensory functions were improving and had reached a marked degree of intensity which had been little lessened

in the five years that had elapsed. He had noticed that the pain was intensified by all sorts of stimuli, such as contact of his clothing with the affected side. Especially deep pressure evoked unpleasant pains and a sensation as if a thousand needles were radiating throughout the limb that was squeezed. For that reason, he avoided shaking hands as far as possible.

Examination revealed a man very well preserved for his age. The tendon reflexes on the right side were hyperactive, but there was good motor function on that side and no sign whatsoever of aphasia. Appreciation of joint movement, vibration and the estimation of weights was almost abolished on the right side. The patient retained some degree of tactile, pain and thermal sensibility. However, the threshold to stimuli was definitely increased. Interpretation of results of tests was difficult because of the markedly effective reaction to all stimuli. A pin prick of the arm, for example, might not be felt at first, but on stronger stimulation was felt as an intense burning pain that radiated up the whole arm into the face. Thermal sensibility was poorly felt until the testing apparatus was made extremely hot or cold; then, the pain was described as being very disagreeable. Tactile sense was the most affected and the lighter degrees of touch were not appreciated at all. Localization of the point of stimulus was practically lost. The patient stated that the only improvement that had occurred in recent years was in the motor functions.

Lesions of the Cerebral Cortex. There has been some difference of opinion on the question of pains arising from cortical lesions. Holmes and Head, for example, have insisted that there is little if any, representation of pain in the cortex and that the thalamus is the essential organ for the reception of impulses carrying affective tone. Corresponding to this, they believe that sensibility to pain is the least altered of all sensibility by destructive cortical lesions. On the other hand, among numerous other observers, including Minkowski, Piéron, Foerster, and Wilson, it is admitted that sensibility to pain has at least some representation in the cortex. Accordingly, they believe the cortical destructive lesions may materially influence the sensibility for pain and that irritative lesions may produce unpleasant sensations, if not actually painful, at least intensely disagreeable. One phase of the problem was investigated by Cushing twenty years ago, with negative results as far as pain is concerned. He stimulated with faradic current the cortex of the postcentral gyrus in two patients who had full consciousness. In one, a sensation described as numbness and, in the other, a tactile impression was felt in the hand of the opposite side. Pain was not complained of by either patient. On the other hand, Foerster, with the same method of electrical stimulation of the postcentral gyrus and superior parietal lobule, claims definitely to have produced painful and disagreeable sensations in various parts of the body on the opposite side. He further stated that pathologic lesions of the cortex can and do produce painful sensations. Clinically, however, it is not often that pathologic irritative lesions produce any marked degree of pain and seldom is it continuous as in that produced by lesions in the thalamus and in levels below it. More often the pains so produced are paroxysmal and appear as a sensory component preceding a Jacksonian or general convulsion. Sensory auras in the

form of tingling sensations, a sensation of formication, wavelike sensations, feelings of constriction, and, according to Foerster, deep, dull pains, may appear in a limb or in one side of the body before convulsive movements begin. It is also common knowledge that painful auras in the form of abdominal pains, especially in children, frequently usher in general convulsive seizures or attacks of petit mal. Foerster mentioned the case of a patient who had pains in the bladder and rectum as an aura preceding Jacksonian attacks. Pains rarely appear in lesions of the subcortical white matter, although cases of this have been reported by Weisenburg and by Mills. In the following case, a tumor involved the cortex and subcortical white matter, apparently sparing the optic thalamus. Although an exact anatomic relationship cannot be determined in infiltrating tumors, it is worth reporting because of the severe pain that accompanied its course.

CASE VI.—A woman, aged forty-three years, was brought to the Mayo Clinic, October 11, 1921, because of pain and weakness in the right arm and leg and the right side of the face. Fourteen months previously, while apparently well, she suddenly had been taken with jerking of the muscles of the right arm, face and jaw, in the order mentioned, and she had suffered loss of speech. This lasted only a few minutes but similar attacks had recurred intermittently for nearly two days, and her speech had been very badly affected for that time. There had not been residual weakness, and within a few days after attacks had ceased her speech had cleared up. About the time of the onset of these jerkings she had noticed a burning, aching, full sensation over the right side of the face, which had been constant ever since. Two or three months later the attacks had been repeated and had been followed this time by clumsiness of the right arm, so that she had dropped objects from the hand and had had difficulty in writing. The unpleasant sensation on the side of the face now had passed into the right arm and she had complained of it feeling hot and swollen. Five months from the period of onset, because of the pain and clumsiness in the right arm, a cervical rib had been removed by a surgeon elsewhere. Several weeks afterward she had had, for the first time, general convulsions and had suffered from headaches which had been present chiefly in the morning and had been felt above and behind the left ear. Prior to the attacks of jerking, which never had been very severe, she had experienced a feeling of terror and as if she were going to be hurried away somewhere without her volition. A year from the onset of the trouble the clumsiness in the arm had progressed to the state of definite weakness, and this rapidly had increased, spreading to involve the right leg a few weeks before admission to the Clinic. The pain previously experienced in the arm and face had spread to the leg and she had noticed diminished sensation in the whole region. She was not sure as to when this sensory disturbance first had appeared, but a few months before she had burned her arm severely on the stove without any very marked pain. The headaches had been getting quite severe, mentally she had become more dull, and her speech had become definitely impaired during the last few weeks.

On examination, the patient had obvious aphasia, which, however, was mild in degree and more in the character of hesitation and stumbling than complete loss of speech. Hemiparesis was present on the right side, more marked in the face and arm and to a less degree in the leg. She was still able to walk around but dragged the leg while doing so. There was a moderate degree of diminution of pain, and thermal and tactile

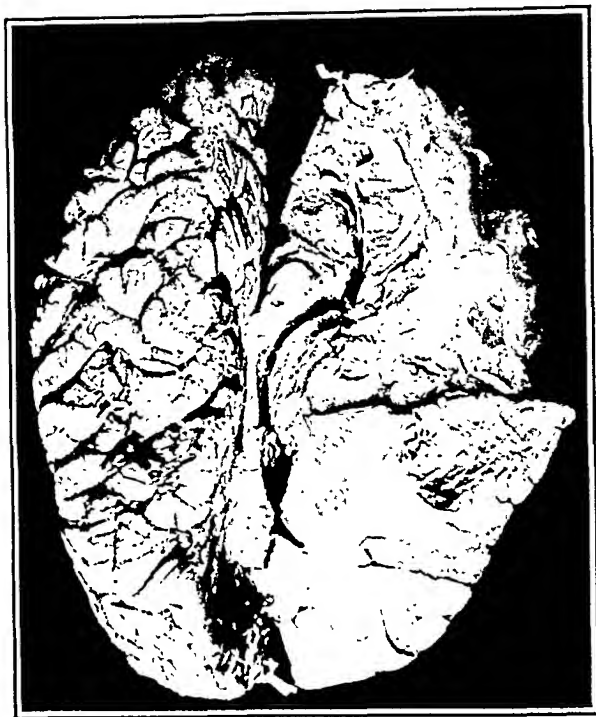


FIG. 3.—Horizontal section of the brain showing tumor involving the cortex and subcortical white matter; the thalamus is apparently intact.



FIG. 4.—The inferior surface of a horizontal section of the left hemisphere of the brain just above the corpus callosum. The tumor was at its greatest diameter here and involved the cortex in front of and behind the central sulcus.

sensibility over the whole right side without any exaggerated responses. This was not dissociated and seemed to be more severe in the extremities of the limbs, from the elbow and knee down. Joint and vibration sensibility were lost in the upper and lower extremities and complete astereognosis was present in the right hand. The corneal reflex was diminished on the right side. During examination the patient was very emotional, cried frequently, and seemed to be greatly disturbed because of difficulty in speaking. On that account also it was difficult to test her sensations adequately. She had numerous attacks of jerking similar to that with which the trouble had begun. They were not Jacksonian in character, but consisted of intermittent twitchings of the whole right upper extremity, without any order of march. She complained bitterly of constant swollen, hot, full, aching sensations in the whole right side of the body. A diagnosis of tumor in the left sensorimotor cortex was made.

Subtemporal decompression was done, November 14, 1921. The cortex had changed in color and appearance in the region of the central sulcus and it was cystic and fluctuating to touch. The patient died the following day.

At necropsy a soft, degenerating, infiltrating, cystic tumor was found. It was about 6.4 cm. in its greatest depth, and it involved the motor and sensory parts of the cortex as well as the subcortical white substance. Anteroposteriorly it was 5.6 cm. long and involved areas in front of and behind the central sulcus about equally. Above, it reached nearly to the superior margin of the hemisphere, but it did not extend below the lateral fissure or involve the temporal lobe to any marked degree. Medially and above, it reached the level of the lateral wall of the lateral ventricle, but below, it did not extend very deeply and it seemed to spare the thalamus. Microscopic examination of sections taken from the motor and the sensory cortex showed dense infiltration by tumor cells which in places reached the pia mater. Some of the cortical layers were completely destroyed. Sections taken from different portions of the thalamus did not show signs of tumor. The histologic diagnosis of the tumor was spongioblastoma multiforme (Figs. 3 and 4).

Summary and Conclusions. Some of the conditions involving the central nervous system that are productive of pain have been discussed. An attempt has been made to confine discussion to those wherein only the brain and spinal cord have been affected. Lesions of the sensory roots of the spinal and cranial nerves and all peripheral nerves are not discussed. The suffering induced in most of the cases described had been intense, and diagnosis in a few was extremely difficult in the early stages of the disease. The central site of the disease process represents a serious difficulty in attempts at therapeutic relief and as a whole such conditions are not easy to deal with from the diagnostic standpoint. The theories concerning the explanation of the phenomena of pain are complicated and are not based on a sure foundation. For this side of the question, reference may be made to Head, Foerster and Wilson's views on the subject. Clinically, the problem of pain of central origin is interesting; infrequent as its occurrence may be, it well repays study and observation.

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SEASONAL INCIDENCE AND STUDY OF FACTORS INFLUENCING THE PRODUCTION OF ONE THOUSAND RECURRENCES OF GASTRODUODENAL ULCERS IN EIGHT HUNDRED PATIENTS.*

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BEING particularly interested in the study of ulcer for a number of years, and with some special opportunities for studying it in all of its phases both in America and abroad, I have been impressed by certain important features that were common to all of these cases—characteristic types of pain and its relation to meals, seasonal relationship, the intermittency of the recurrences and the constitutional characteristics, particularly facial expression of the patients.

In this article I shall discuss the study of ulcers merely in one of its phases, namely, the rôle of factors which influenced the production of recurrent attacks of gastroduodenal ulcers, based on 1000 recurrences in 800 patients. In my observations and investigations I have made every effort to obtain a detailed clinical history, not alone of my old patients who returned with recurrences of their symptoms, but also of patients consulting me for the first time, who were formerly treated by other physicians.

Seasonal Incidence. The data of seasonal incidence given in Chart I represents not only recurrences which were under my observation, but also past recurrences, obtained from the clinical histories of the patients.

In present recurrences the following percentages were obtained: fall, 42 per cent; spring, 35 per cent; winter, 19 per cent; summer, 4 per cent; whereas, the percentages of past recurrences were: fall, 46 per cent; spring, 41 per cent; winter, 6 per cent; summer, 7 per cent.

From the above, we note that the results for the fall and spring are about equal, in past and present recurrences, but that they vary slightly as regards the winter and summer seasons. Present recurrences having been based on a more accurate and detailed study may, therefore, be accepted as more exact.

Monthly Incidence. A careful analysis of the frequency of recurrences per month was also made, and is indicated by the dark curve in Chart II. Commencing with the month of January, we note a slight rise in recurrences to 9 per cent, with a decline to 6 per cent during the month of February. Early in the month of March there is a rise to 12 per cent, with minor fluctuations, which remain more or less constant during the months of April and May. Beginning with the month of June, a decided decline to 1 per cent is observed,

* Read before the Eastern Medical Society, New York City, May 10, 1929.

remaining thus through the months of July and August. At the end of this month the percentage rises, reaching its highest point of 20 per cent by the beginning of the month of September. During the month of November there is a gradual decline to 7 per cent, and thereafter remaining stationary throughout the winter months.

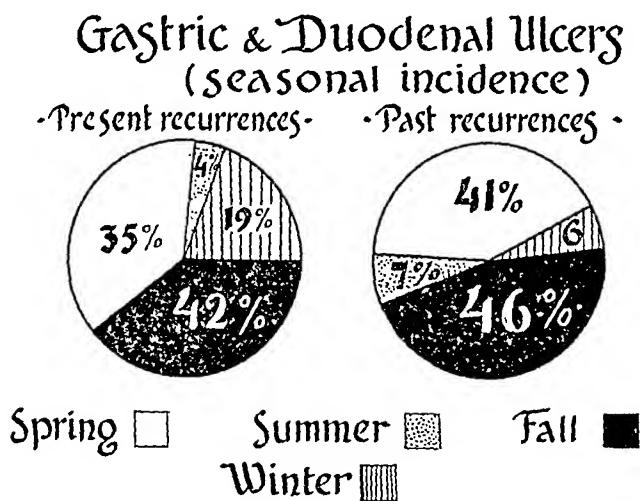


CHART I.

According to the above findings, most of the recurrences occurred during the months of September and May, and a moderate number during the months of March and October. There was a minimum percentage of recurrences in the months of June, July and August.

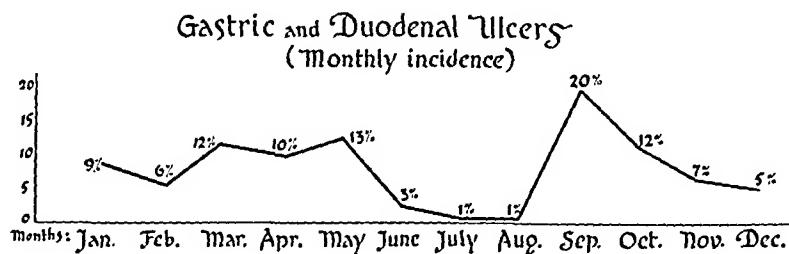


CHART II.

Weekly Incidence. In Chart III two curves are plotted, the light curve representing the months and the heavy curve the weeks. Roman numerals indicate the division of months into weeks. Certain characteristic points in the weekly incidence can be noted from this chart: There is a sudden rise in recurrences from the beginning of the fourth week in February, including the first week in March, which corresponds to the increase in percentage in the monthly incidence. During the fourth week in May until the second week in June there is a decided decline, remaining constant throughout the summer months. Commencing with the third week

in August, there is a gradual rise until the maximum number of recurrences is reached during the second week in September.

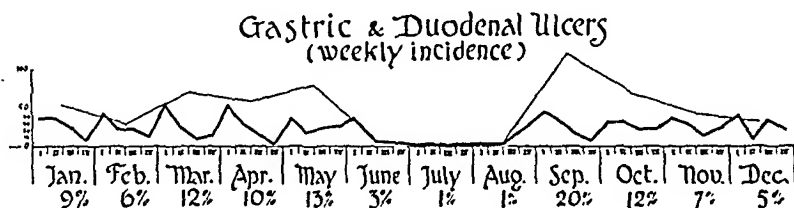


CHART III.

From the above study it is obvious that there are certain definite seasons, namely, the fall and spring, during which the greatest number of recurrent attacks occur. I should like here to advance several reasons which will probably explain this seasonal incidence.

In the summer the ulcer patient leaves the city for a vacation and rest in the country. His life at this time is usually well balanced, his diet regular and he undergoes a minimum of fatigue and exertion during this period. Patients subject to chronic ailments such as pulmonary or cardiac diseases or those susceptible to colds, hay fever or asthma are generally relieved at this time.

With the advent of the fall the patient returns to the city, in order to resume his business activities. In contrast to the rest and relaxation which he enjoyed in the country, he now feels the nervous strain of his new duties and surroundings. These have a marked effect upon the patient who is extremely susceptible to change. His meals become irregular and hurried, and the raw fruits which are now in season do not agree with him. The rainy season too, which now commences, has an effect upon those patients who are subject to chronic diseases and colds.

In the spring the weather changes intermittently from cold to mild, and inasmuch as the patients remove their winter apparel early in the season, before the temperature is yet stable, they are liable to have more colds. Those patients who suffer with hay fever are also greatly annoyed at this time of the year. Then, too, the diet, which is now constituted largely of fresh raw vegetables, seems to have a disadvantageous effect on the ulcer patient.

The Rôle of Factors in the Production of Recurrences. In Chart IV the percentage incidence with reference to colds, psychic load, diet and external pressure is shown.

Colds. Colds are the most important factor, being present in 57 per cent of all recurrences. I was interested also in the degree and intensity of colds, and found in my analysis that the mild cold with the sneezing and running nose constituted the highest percentage; the more severe cold, accompanied by respiratory ailments as bronchitis and sore throat, a moderate percentage and the remaining

small percentage were attributed to the more acute conditions, such as grippe and influenza.

During the months of January and February, 1929, I had the opportunity of studying the effect on the recurrent attacks of gastro-duodenal ulcers, of the recent epidemic, which reached the shores of New York and New Jersey about the months of December, 1928, and January, 1929.¹ I was impressed by a number of my old patients, who returned with recurrences, who never before had attacks during this season of the year.

Role of Factors in Production of Gastro-Duodenal Attacks

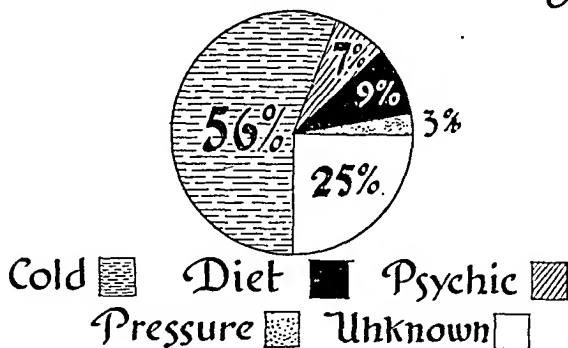


CHART IV.

Upon investigation, I learned that each of these patients, previous to reporting to the office, had been ill with grippe or influenza, the diagnosis having been made by the family physician. I also observed that their gastrointestinal symptoms and the duration of their recovery varied with the severity or mildness of the influenza attack.

Diet. Diet as a cause was found in only 9 per cent of the recurrent attacks, a surprisingly small percentage, in view of the fact that the treatment of ulcer is essentially dietetic.

Psychic Load. Psychic influences, such as anger, shock, emotion and business reverses, play a causative rôle in the development and recurrent attacks of ulcer, the percentage as shown in the above chart being 7 per cent. Several of my cases deserve special mention here, as they represent the type of individual who reacts particularly to emotional disturbances.

One case is that of a broker who reported to my office with a gastroduodenal recurrence induced by sudden fluctuations in the Wall Street market; another patient had a severe attack immediately after suffering heavy losses on the race track; a professional speaker and a musician both had recurrences of symptoms whenever they developed stage fright on appearing before an audience.

Extreme depression caused by the death of a relative, or great happiness, in many cases, brought on an attack. In each instance the onset, which may have been in any form, was necessarily very sudden and not gradual.

External Pressure. External pressure is represented here in only 3 per cent of the gastroduodenal recurrences. A few years ago I made a special study of this factor with regard to the effect of the pressure of belts on ulcer patients.² My investigation of this study, which I presented in a separate article, was conducted along the following lines:

A number of patients were selected and divided into two groups: Group I consisted of those who wore suspenders during the period of observation, while Group II was composed of those whom I directed to wear belts. I laid particular stress in this study on ascertaining the difference, if any, as to the time required for the disappearance of the symptoms and also as to the number of recurrences.

On the whole, the symptoms were eliminated more quickly, and there were less recurrences in the suspender group than in the group which wore belts. I was convinced that there is a definite advantage in having the patient wear suspenders instead of a belt.

In spite of the careful and detailed analysis which was made, 25 per cent of the cases still remained in which no definite cause for the recurrence could be ascertained.

Our findings in a study of the seasonal relationship and the probable cause of recurrences in a follow-up of 100 cases of gastroduodenal ulcer³ were about the same as those given here.

Summary. 1. There are certain definite seasons, namely the spring and fall, during which most of the recurrences of gastroduodenal ulcers occur.

2. The largest number of recurrences occur during the months of September and May, a moderate number during March and October and a minimum percentage during the months of June, July and August.

3. There is a rise in recurrences beginning the fourth week in February, including the first week in March; a decline during the fourth week in May until the second week in June; a gradual rise commencing the third week in August until the second week in September, at which period the maximum number is reached.

4. Colds, diet, psychic load and external pressure are several factors which play an important rôle in the production of recurrences.

5. In 25 per cent of the cases there are no definite factors to which the recurrent attacks of gastroduodenal ulcers can be attributed.

Comment. There are certain critical periods for each individual ulcer patient and recurrent attacks will generally occur at a given time in these patients. It is, therefore, important to ascertain the exact critical period of the patients, in order to prevent these

recurrences. Each patient should be instructed to report for treatment a few weeks prior to the probable period of the recurrence, even though he may be feeling well at that time.

In following this outline of treatment, I have been successful in preventing gastroduodenal recurrences in a number of my patients.⁴

Only when the patient learns to follow the above instructions, can we hope to prevent recurrences and ultimately obtain better results in the treatment of gastroduodenal ulcers.

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AMOEBIC ABSCESS OF THE LIVER: REPORT OF FOUR CASES IN THE NORTH TEMPERATE ZONE.*

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ABSCESS of the liver due to *Endamoeba histolytica* in the North Temperate Zone is of sufficient rarity to warrant reporting 4 cases which were observed in 1928 at The Mayo Clinic. During the preceding seven years only 6 other cases of amoebic abscess had been recorded at the Clinic although search for the amoeba had been made in other cases in which abscess of the liver had occurred.

The disease has been the cause of serious concern in the tropics and it is by authorities working there that knowledge of this complication of endamebiasis has been advanced. It is largely due to Rogers that the more effective management of amoebic abscess of the liver has been established. In a group of 2516 cases, he found a mortality of 56.7 per cent, but after introduction of the combined treatment by emetin and aspiration, the mortality in 111 cases was 14 per cent. He quoted Chatterjee, who later recorded only 1.6 per cent mortality in 186 cases. The splendid work of Ludlow in Korea should be noted; he had a mortality of 8.8 per cent in 160 cases. Closer study of his report shows that in 43 cases in which aspiration and emetin were employed, the mortality was only 2.3

* Submitted for publication June 4, 1929.

per cent. From northern Africa comes another excellent report by Lacase who had a mortality of 8 (3.1 per cent) in 252 cases. Lacase advises emetin and aspiration but does not hesitate to undertake an open operation in suitable cases.

The abscess may be single or multiple. Lacase noted that the abscesses were multiple in 53 cases, about 20 per cent, of a series of 252 cases of amoebic abscess. Ludlow noted that multiple abscesses were present in 10 per cent of 160 cases. McGlannan quoted Rogers, who holds that there were single abscesses in 51 per cent of a series of cases, two or more large abscesses in 25.8 per cent, and one large abscess together with several small abscesses in 24.4 per cent. Ludlow emphasized alcohol as a possible predisposing factor, for white people of the tropics are more subject to abscess than natives, and especially is this true in alcoholic patients.

An antecedent history of diarrhea usually is obtained, and was elicited in the 4 cases of the group to be reported. Cort reported hepatic involvement in 97 cases of 530, and in this 97, there was a history of diarrhea. Ludlow elicited a history of diarrhea in 137 of 160 cases, but he observed that diarrhea is such a common occurrence in the tropics that an occasional spell of diarrhea may be forgotten.

Report of Cases Observed in The Mayo Clinic. CASE I.—A man, aged twenty-three years, a resident of Indiana, said that for several months he had had an occasional spell of mild diarrhea. Twelve weeks prior to admission to the Clinic pain had appeared in the right lower part of the chest and upper right portion of the abdomen. This had been accompanied by fever and loss of weight.

General examination revealed nothing of moment other than tenderness in the upper right quadrant of the abdomen. There was leukocytosis of 29,000 with 16 per cent lymphocytes; 7.5 per cent large mononuclear leukocytes; 2.5 per cent transitional cells, and 74 per cent neutrophils. One examination of stool gave negative results and the roentgenogram of the chest did not reveal abnormality.

Right pleurocentesis was done and in the aspirated fluid *Endamoeba histolytica* was identified. Treatment by means of 0.65 gm. (10 grains) emetin hydrochlorid hypodermically and 6 gm. of treparsol (formin derivative of meta-amino-para-oxyphenyl-arsenic acid) orally, both in divided doses was instituted. During this treatment aspiration was done several times, as there proved to be a large abscess of the right lobe of the liver which was of such size as to all but preclude possibility of its being absorbed. At the end of thirty-three days' hospitalization the patient was dismissed in excellent condition. Further treatment, in divided courses of auremetin (hydrogen periodid of emetin and auramin) and treparsol was advised.

CASE II.—A man, aged twenty-five years, a resident of Indiana, three months prior to admission had had bloody dysentery which persisted with varying intensity. He had begun to lose strength, and rather abruptly had begun to cough up blood and foul sputum. Six weeks prior to admission resection of a rib in the lower right part of the thorax had been done, with a resulting discharge of bloody pus. On admission, there was still diarrhea, but the most striking feature was the constant cough and raising of dark, bloody, chocolate-colored pus. The patient was so weak and dyspneic

that it was difficult to obtain a history. He seemed to be half drowned in the secretions of the lungs.

General examination revealed in the right lower part of the chest marked dullness which extended almost to the fourth rib anteriorly. A discharging sinus was present in the right side of the chest. The temperature was 103° F. The hemoglobin was estimated at 47 per cent; erythrocytes numbered 3,310,000 and the leukocytes varied from 14,800 to 28,100. Roentgenograms of the chest revealed fluid at the base on the right side.

Because of the pronounced thoracic symptoms, the preliminary impression was that possibly a malignant condition was present. Thoracentesis was done, and growths were not obtained on culture; however, in other cultures, and also by means of smears, *Endamoeba histolytica* was identified. Just prior to this disclosure, *Endamoeba histolytica* was identified in the stools. The usual treatment by emetin and treparsol was instituted. While the patient was under treatment copious, spontaneous drainage developed at the site of the former rib resection and a tube was inserted. The patient's convalescence was gradual at first, but after fifty-three days he was dismissed from the hospital in excellent condition. Further antiamoebic treatment was to be carried out at home.

CASE III.—A man, aged thirty-six years, a resident of Wyoming, had contracted dysentery while in Texas eight months before he was seen at the Clinic. A diagnosis of amoebic colitis had been made and 0.77 gm. (12 grains) of emetin had been administered in divided doses. He had suffered a recurrence in about four weeks and had received 0.77 gm. (12 grains) more of emetin and 10.5 gm. of stovarsol both in divided doses. He had remained free of trouble until two weeks prior to admission, when chills and fever had appeared and pain had developed in the lower right part of the chest. His physician, who had had military service in the Philippines, had aspirated the liver and had identified *Endamoeba histolytica*. He then had referred the patient for further treatment.

On admission the patient had fever and the temperature ranged as high as 101.5° F.; hemoglobin was estimated at 65 per cent. Erythrocytes numbered 3,980,000 and leukocytes 11,700, with a differential count of 26.5 per cent lymphocytes; 2.5 per cent large mononuclears; 69.5 per cent neutrophils; 1 per cent eosinophils and 0.5 per cent basophils. Stools contained *Endamoeba histolytica* and *Giardia lamblia*.

Roentgenographic studies of the chest and colon and a proctoscopic examination, gave negative results.

The patient did not seem acutely ill, so that medical management, without aspiration, was carried out. He received 0.5 gm. (8 grains) of emetin and 6 gm. of treparsol, both in divided doses. At the end of nineteen days of hospitalization, he felt very well and was permitted to leave. He remained well only six or seven weeks, when the diarrhea recurred, and ten days later the pains in the hepatic region returned. On readmission, treatment consisting of 0.2 gm. (3 grains) of emetin, 4 gm. of treparsol, and about 20 gm. of yatren, all in divided doses, was administered. In spite of this he continued to fail. The temperature rose to 103° and leukocytosis of 14,000 cells was present. Through a posterolateral incision, about 1 liter of thick, dark, odorless pus was drained and smears made from the pus revealed *Endamoeba histolytica*. Postoperative convalescence was uneventful except that the parasite persisted in the pus from the draining sinus. Irrigations with solution of quinin then were advised and persistence in taking interrupted courses of emetin and treparsol was urged. At the time of the patient's dismissal his condition was satisfactory, although there was still slight drainage.

CASE IV.—A woman, aged forty-seven years, a resident of Illinois, during the two years previous to admission to the Clinic had had an occasional spell of mild dysentery which had seemed to clear up without any particular medication. For about ten years she had had attacks of right upper abdominal pain associated with fever.

On admission, she complained of pain in the area of the liver and tenderness in this region was elicited. Her temperature was as high as 103°. The hemoglobin was estimated at 42 per cent. Erythrocytes numbered 3,000,000 and leukocytes 14,000 with a differential count of lymphocytes, 9 per cent; large mononuclear leukocytes, 3.5 per cent; transitionals, 2 per cent; neutrophils, 84 per cent; basophils, 0.5 per cent. Two examinations of stools revealed only *Endamoeba coli*. Roentgenographic studies of the chest, colon and stomach gave negative results.

A positive diagnosis was not possible, although there was some reason to think that the patient might be suffering from empyema of the gall bladder or abscess above or below the liver. While she was under observation, in the hope that the acute process would subside and permit a more favorable time for exploration, a course of emetin and treparsol was administered. There ensued an abrupt and spectacular response to treatment, so that, after the completion of a course of 0.65 gm. (10 grains) of emetin and 4.25 gm. of treparsol, both in divided doses, the patient was permitted to return home and there to carry out further antiamoebic treatment.

Comment. This group of 4 cases presents several of the unusual phases of the management of amoebic abscess of the liver, both from the diagnostic as well as from the therapeutic standpoints. Objection might well be made to considering Case IV as an instance of hepatic abscess, especially as a case of abscess due to amoeba. There is no positive confirmation of the diagnosis by laboratory methods but one would not expect so spectacular and so abrupt a response to treatment if the symptoms were due to a pyogenic infection of the gall bladder or liver. The indeterminate features of this case and the history of diarrhea fully justified the therapeutic trial. Certainly 0.24 to 0.40 gm. (4 to 6 grains) of emetin hydrochlorid can be given in divided doses with little or no risk and if the symptoms are due to the amoeba, there is almost always a decided response. To carry out a prolonged therapeutic trial may prove unwise, but a short course of treatment may prevent many further difficulties. If such a large abscess is present in the liver that it cannot be absorbed, aspiration can be carried out with little or no risk, and from the aspirated fluid, smears and cultures may be made and examined for *Endamoeba histolytica*.

Case I illustrates the effect of aspirating a large abscess, and aspiration was repeated several times in this case. Antiamoebic treatment in such a case is of the utmost necessity; yet it is expecting a great deal to assume that the body can absorb as large an accumulation of pus as was present.

Case III would seem not to conform with the statement of Rogers that abscess develops only in untreated or in insufficiently treated cases. A reasonable amount of antiamoebic treatment had been administered early in the stage of dysentery, before the patient

arrived in Rochester, yet the treatment can be criticized on the ground that follow-up examinations were not made and that the treatment was not varied. Prior to his first admission, therefore, the patient can be considered to have had insufficient treatment. During his first period at the Clinic, his response to treatment was as striking as that of the patient in Case IV. Further treatment was advised. However, symptoms relative both to the bowel and to the liver recurred, and this in spite of treatment that had been so intensive that complications such as neuritis were feared. At this stage, yatren was tried and a small amount of emetin and treparsol was given without benefit. Surgical drainage of the huge abscess demonstrated why medical management no longer would be of help, and yet the development of such an abscess, under intensive treatment, gives cause for anxiety. Such cases must be infrequent, and fortunately so. Suitable drainage followed by careful, interrupted treatment eventually should produce a cure. It is possible that the abscess was present at the first admission and that anti-amœbic treatment was sufficient temporarily to halt the process but that the disease had established too firm a hold on the liver to be aborted. Also, aspiration at that time might have obviated the necessity of the patient's returning the second time.

Case II is the most remarkable one of this small group. On first appearance the patient seemed to be not much more than able to keep alive. The constant productive cough and dyspnea which all but precluded speech and prevented his lying down, dominated the picture. There occur many scattered references to rupture of amœbic abscess of the liver through the diaphragm and finally into a bronchus. The case reported here, therefore, is by no means unique. The size of the abscess was such that antiamœbic treatment would not have sufficed. Fortunately, there was a sinus through which adequate drainage established itself; also the patient had been fortunate in not having suffered even more serious difficulties at the time of the resection of the rib. It is conceivable that the resection may have been a factor in the rupturing of the hepatic abscess into the bronchial tubes, although this would probably have occurred, due to the protracted illness of the patient.

Summary and Conclusions. 1. Amœbic abscess of the liver in the North Temperate Zone occurs infrequently.

2. The recognition of *Endamœba histolytica* as a possible cause of hepatic abscess must not be overlooked. Failure to recognize it may lead to serious complications, and abdominal exploration in such cases is dangerous.

3. Treatment of amœbic colitis must be carefully and thoroughly carried out and extended examinations of stools should be made. This should prevent the development of hepatic abscess except in the occasional case.

4. An antecedent history of diarrhea is not always obtained, although it was elicited in the four cases reported here.

5. Tenderness in the region of the liver, fever, and leukocytosis are the usual features that direct attention to hepatic complications in a case of endamœbiasis.

6. Emetin and treparsol, in conjunction with as conservative an operation as possible, preferably aspiration only, is the method of choice in dealing with amœbic abscess of the liver.

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REVIEWS.

PRACTICAL LOCAL ANESTHESIA. By ROBERT EMMETT FARR, M.D., F.A.C.S. Pp. 611; 268 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1929. Price, \$9.00.

THIS, the second edition of the author's work on Practical Local Anesthesia, is a distinct addition to the literature. The so-called melodramatic features, such as photographs of "smiling patients" which seem to be indicated from the educational standpoint in the first volume, have been deleted and their place taken by numerous well-executed drawings following the technique of the Brödel school. The text is valuable alike to the beginner and the experienced operator. If an objection could be offered it would be directed against the including of case reports. A man with the experience of the author does not need such reënforcement to his text. The work is a thoroughly good one.

E. E.

LABORATORY METHODS OF THE UNITED STATES ARMY. Edited by CHARLES F. CRAIG, M.A., M.D. Pp. 696; 9 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$3.50.

STARTING as a war manual, this useful little book edited by a well-known authority, now takes its legitimate place in the civilian laboratory. With new sections in this edition on Protozoölogy, Helminthology, Entomology and Veterinary Methods, though small in size, its scope is considerable. Clinical Pathological Methods (218 pages) and General and Special Bacteriological Methods (210 pages) comprise the bulk of the book, but in addition to the new sections mentioned, there are also parts on examination of water, sewage, meat and dairy products, alcohols, also on disinfectants, water sterilization and pathological (really postmortem) methods.

While completeness can hardly be expected in a production of this kind, one misses a number of desirable methods; in the blood section, for instance, I find no reference to such simple useful tests as the erythrocyte fragility, the reticulocyte count and the sedimentation time. While useful up to a certain point, then, such small manuals cannot be expected to give as satisfactory service as the larger books.

E. K.

HUMAN HELMINTHOLOGY. By ERNEST CARROLL FAUST, PH.D.,
Pp. 616; 297 illustrations. Philadelphia: Lea & Febiger, 1929.
Price, \$8.00.

A WELL documented volume, presenting a wealth of information on the parasitic helminths of man. Introductory remarks include general discussions of the history and modern development of the subject, parasite and host adaptation, factors influencing parasite distribution, and specific names as determined by the International Code of Zoölogical Nomenclature. The taxonomy and biology of the large groups are next considered, followed by detailed accounts of life cycles, diagnosis, therapeusis and prophylaxis of both important and incidental species. Chapters on special laboratory technique and methods of diagnosis, and on the intermediate hosts of the worms are included. The text is well illustrated with original photographs and drawings, certain life cycles being presented graphically. Although much is included that will interest only the specialist, the book will be a valuable aid to the student, the clinician and the pathologist.

H. R.

STERILIZATION FOR HUMAN BETTERMENT. By E. S. GOSNEY, B.S., LL.B., and PAUL POPENOE, D.Sc. Pp. 202. New York: The Macmillan Company, 1929. Price \$2.00.

CALIFORNIA has conducted an experiment of the utmost importance in application of modern surgery to race betterment. More than six thousand mental defectives have been legally sterilized in that state over a period of twenty years. The surgical, biological and social data of that large scale experiment have been collected, and published in technical journals. The present book represents a summary of the chief findings, written in very readable form indeed. Bibliography and summary of the present legal status of sterilization are appended.

If the intrinsic interest of the California sterilization program were not in itself sufficient, it would become so through a recent decision of the United States Supreme Court sustaining a state sterilization law, and asserting that "three generations of imbeciles are enough."

S. M.

THE BLOOD PICTURE. By PROF. DR. VICTOR SCHILLING. Translated and edited by R. B. H. GRADWOHL, M.D. Seventh and Eighth Revised Edition. Pp. 408; 48 illustrations. St. Louis: The C. V. Mosby Company, 1929.

As is to be expected in a book by Schilling, the blood smear, the hemogram and the thick drop are especially emphasized; in fact,

ordinary leukocyte, erythrocyte and hemoglobin determinations are relegated to the "auxiliary method" group. While such strivings toward greater technical simplicity may meet with favor in Germany the trend in this country is definitely toward the elaboration of laboratory diagnostic methods, especially when, as in this case, facts of value are lost in the simplifying process. Emphasis is also placed on tropical methods (from which the book in the original German grew), on vital stains, and on Schilling's new nonspecific "guttadiaphot" test. The presentation of the leukocytic nuclear shift is thorough, well done and extremely valuable, as one would expect from its most active exponent. No one reading this section should remain in doubt as to the value of the method to clinical medicine and surgery. This country has hitherto been slow to appreciate its advantages.

E. K.

MODERN METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., with Chapters on Special Subjects by various collaborators. Third edition. Pp. 815; 95 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$10.00.

A BRAVE attempt to include in one volume every department of medical therapeutics. In this edition, the sections on diathermy, liver in anemia, iodine in goiter, and nonspecific protein therapy have been revised and several new drugs added. Even a reasonably complete presentation of such a wide range could not be expected and is not found. The lack is at least partly compensated for by a vigorous, interesting style of presentation which does not hesitate to call a spade a spade.

E. K.

THE FEMALE SEX HORMONE. By ROBERT T. FRANK, A.M., M.D., F.A.C.S., Gynecologist to Mt. Sinai Hospital, New York. Pp. 298; 86 illustrations and 36 graphs. Illinois: Charles C. Thomas, 1929. Price, \$5.50.

THIS monograph presents from both a laboratory and clinical standpoint the results of many long and painstaking researches on the internal secretions of the female reproductive organs. The first section of the book deals with the history of the biologic, pharmacologic and chemical investigations, and evaluates and correlates many partly related studies. Here, also, is found the technique for the author's blood test for the female sex hormone.

The second, or clinical, section deals with a study of the blood of five hundred women by this test. The results are classified under various functional and clinical headings, and suggestions are given for the study and treatment of these conditions. Full proof is

furnished for the author's nihilism in regard to present-day therapy by ovarian substances, and other related products, as recommended by biologic manufacturers. It is only to be hoped that a therapeutic agent for hypofunction of the ovaries as reliable as the proposed diagnostic test is simple will soon be forthcoming. There is a copious bibliography attached to each section, and an authors' index. The book closes with a review and summary of the present status of the female sex hormone. This monograph will undoubtedly be of great interest to all physicians concerned with the endocrinology of the female.

P. W.

DE OCULIS. By BENEVENUTUS GRASSUS. Translated by CASEY A. WOOD, M.D., LL.D. Pp. 101; 5 illustrations. California: Stanford University Press, 1929. Price, \$5.00.

BENEVENUTUS GRASSUS, also known as Benevenutus De Salern or Hierosolimitans, probably a Jewish physician of the eleventh century wrote a practical treatise on diseases of the eye that was highly esteemed by medieval surgeons, and for five hundred years was the most popular manual on the subject. It also has the distinction of being the first printed book on ophthalmology, the incunabulum having been printed at Ferrara, as the translator of the present book shows in his introduction, in 1474. There are 22 manuscripts and about 18 printed editions of this text, though but very few copies are extant, a list of which are given at the end of this volume. Dr. Casey Wood's translation is welcome addition to medicohistorical literature, especially with its instructive introduction and in the pleasing form that the Stanford University Press has given it.

E. K.

TUBERCULOUS INTOXICATION. By JOSEPH HOLLOS, M.D., Pathologist of St. Vincent's Hospital, Staten Island, New York. Pp. 132. New York: William Wood & Co., 1928. Price, \$3.25.

THE author believes that an antitoxic and lytic immunity develops in latent tuberculosis and that hypersensitiveness is brought about by the liberation of endotoxins from the dissolved tubercle bacilli. As a consequence of this hypersensitiveness a condition of tuberculous intoxication results, which manifests itself in disturbances of the endocrine system, neurasthenia, rheumatism, epilepsy, thyroïsis and in various other ways.

According to Dr. Hollos the tuberculous intoxication may be cured by the use of Spengler's immune blood, which is prepared by hemolysing the washed red blood cells of immunized rabbits. This treatment has been discredited and no critical evidence is presented in this volume to justify its use.

J. A.

A STUDY OF MASTURBATION AND SEXUAL LIFE. By JOHN F. W. MEAGHER, M.D., F.A.C.P. Neurologist to St. Mary's Hospital, Brooklyn; Consulting Psychiatrist to Kings Park State Hospital; and so forth. Second edition. Pp. 130. New York: William Wood & Co., 1929. Price, \$2.00.

THIS author speaks with pride of the favorable reception accorded the first edition and the subject certainly merits scientific consideration, since: "Not only physicians, but clergymen and teachers are often consulted by parents, and by the youths themselves, for advice in regard to disturbances which they attribute to this habit."

N. Y.

AN INTRODUCTION TO PHARMACOLOGY AND THERAPEUTICS. By G. A. GUNN, M.D., Professor of Pharmacology in the University of Oxford. Pp. 213. New York: Oxford University Press, American Branch, 1929.

THIS little book is essentially a pocket edition of Cushny's textbook of pharmacology. Brevity is achieved by selection of salient features, which are thoroughly treated, and by omission of controversial points and of the evidence upon which current ideas are based. The book provides an admirable birds-eye view of the essential features in the actions of practically all important drugs. It was not intended to replace more comprehensive textbooks, but to provide a background for them. It is heartily recommended to the student, intern, and physician who wishes to reestablish his conceptions of drug actions.

C. S.

THE CONQUEST OF CANCER BY RADIUM AND OTHER METHODS. By DANIEL THOMAS QUIGLEY, M.D., F.A.C.S. Pp. 539; 334 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$6.00.

THIS book appears to have been written by one intelligent and optimistic, in enthusiastic praise of the virtues of radium in the prevention and cure of malignant tumors.

It contains much that is true and good, and the author and some of his patients are to be congratulated upon the excellent results obtained in many of the reported cases.

But it is clear, from the beginning to the end, that the author's scientific background is somewhat hazy, and his pathology original. In consequence the work is full of categorical statements and dogmatic conclusions that cannot fail to astonish the readers.

To him cancer is not a great unknown disease: he knows all about it. See how he explains it: "The period of development of a

carcinoma in an area where it can be studied through all its various stages, such as a cancer developing on the lower lip, shows that the precancerous disease is a definite injury, a definite poisoning, and a definite infection by extrinsic agents. These agents produce a benign ulcer. During the period of extrinsic influence and the period of benign ulcer, the time element is very much greater than the time element involved in the development of neoplastic tissue, as a parasite, up to the point where pain and bleeding and cachexia lead the victim eventually to die the 'stinking death.'"

See also his final conclusion: "We probably know more about cancer than about any other chronic disease. Instead of being hopeless from the standpoint of cure, *it is probably the most easily and surely curable of any of the chronic diseases.*"

Think of that in the face of the multitudinous controversial questions as to its origin and nature, and especially in view of its ever increasing incidence and appalling death rate! J. McF.

THE ROBERT JONES BIRTHDAY VOLUME. A COLLECTION OF SURGICAL ESSAYS. Pp. 434; illustrated. New York: Oxford University Press, American Branch, 1929. Price, \$13.00.

THIS volume of surgical essays has been contributed to by twenty-four of the great writers of the world who were friends or pupils or who had been associated with him during the World War. The essays are all on clinical subjects of extreme importance to surgeons, internists and orthopedists. Many of these essays are classics and when grouped in one volume as this and prefaced by such a master of diction as Sir Berkeley Moynihan, the whole constitutes a collection that should be of great value to its readers.

The book is nicely made, beautifully edited and abundantly and profusely illustrated. E. E.

SOME PRINCIPLES OF MINOR SURGERY. By ZACHARY COPE, M.S., M.D., F.R.C.S. (ENG.) Pp. 159; 82 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.50.

THE writer has undertaken a difficult task in presenting a work of this character because whatever he includes or excludes in the subject matter there will always be some critics who will criticize omission or commission. He wisely does not claim to have written a minor surgery but has confined his efforts to presenting in detail many of the minor principles that are so often omitted from the larger works as being too unimportant to occupy valuable page space.

To students both undergraduate and postgraduate it can be of great help, especially in the trying days of early practice. The reviewer recommends it as such very highly. E. E.

BOOKS RECEIVED.

NEW BOOKS.

- Clinical Obstetrics*.* By PAUL T. HARPER, PH.B., M.D., Sc.D., F.A.C.S. Pp. 629; 84 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$8.00.
- Hemorrhoids—The Injection Treatment and Pruritus Ani*.* By LAWRENCE GOLDBACHER, M.D. Pp. 205; 31 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$3.50.
- The Treatment of Varicose Veins*.* By T. HENRY TREVES-BARBER, M.D., B.Sc. Pp. 120; 11 illustrations. New York: William Wood & Co., 1929. Price, \$2.25.
- The Surgical Clinics of North America (Lahey Clinic Number)*. Vol. IX, No. 6. December, 1929. Pp. 188; 51 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- The Medical Clinics of North America (New York Number)*. Vol. XIII, No. 3. November, 1929. Pp. 272; 58 illustrations. Philadelphia: W. B. Saunders Company, 1929.
- Coronary Thrombosis: Its Various Clinical Features. (Medicine Monograph XVI.)** By SAMUEL A. LEVINE, M.D. Pp. 178; 85 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, \$3.00.
- Blood Grouping in Relation to Legal and Clinical Medicine*.* By LAURENCE H. SNYDER, Sc.D. Pp. 153; 28 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, \$5.00.
- Progressive Medicine, Vol. IV, December, 1929*. Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 357; 80 illustrations. Philadelphia: Lea & Febiger, 1929.

NEW EDITIONS.

- The Treatment of the Common Disorders of Digestion*.* By JOHN L. KANTOR, PH.D., M.D. Pp. 300; 88 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1929. Price, \$6.00.
- Manual of Midwifery*. By HENRY JELLETT, B.A., M.D. (Dub. Univ.), F.R.C.P.I., L.M. and DAVID G. MADILL, B.A., M.B., B.Ch., B.A.O. (Dub. Univ.), L.M. Pp. 1281; 570 illustrations. Fourth edition. New York: William Wood & Co., 1929. Price, \$10.00.
- An authoritative work with emphasis on the methods of the Rotunda Hospital. New sections have been added on anesthesia, pyelitis, nephritic and preëclamptic toxemia.
- An Outline of Endocrinology*.* By W. M. CROFTON, B.A., M.D. Pp. 163; 53 illustrations. Second edition. New York: William Wood & Co., 1929. Price, \$3.00.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Skin Reactions to Filtrates of Hemolytic Streptococci in Acute and Subacute Nephritis.—During the course of a previous investigation HANSEN-PRUSS, LONGCOPE and O'BRIEN (*J. Clin. Invest.*, 1929, 7, 543) noted that hemolytic streptococci isolated from the tonsils, adenoids or accessory nasal sinuses of cases of acute and subacute glomerular nephritis produced "toxins" which gave skin reactions comparable to those produced by the "Dick Toxin." They noted also that greatest intensity of the skin reactions occurred in those patients suffering from acute and subacute nephritis associated with infections caused by hemolytic streptococci. A systematic study was made of the incidence and intensity of the skin reactions to the bouillon filtrates of hemolytic streptococci in three groups of cases; first, patients with acute and subacute nephritis; second, normal individuals and third, patients suffering from uncomplicated acute tonsillitis. Eighteen strains of hemolytic streptococci were used. They were grown in beef infusion peptone broth. For skin reactions the filtrates were usually employed in 1 to 100 dilutions. When positive reactions were obtainable the dilutions were increased to 1 to 500, 1 to 1000, 1 to 2000. For each test 0.1 cc. of the dilution was employed. Proper controls were used. The skin reactions were observed at the end of eighteen and twenty-four hours and depending upon the size of the diameter of the reaction, they were labeled +, ++, +++, +++++. The reaction of the skin in normal persons and patients suffering from abnormal conditions were as follows: Sixty individuals were tested, 38 of whom gave positive reactions and 15 gave a +++++ reaction. In other words, the patients gave a strong reaction to a dilution of 1 to 100 and of the individuals who gave positive reactions with this dilution, only 9 per cent gave +++++ result with the 1 to 500 dilution. In this control group, the individuals

having tonsillitis or sinusitis gave the strongest reactions. In the group of 27 patients who had nephritis 81 per cent gave positive reactions and two-thirds of the number gave ++++ reactions. These reactions, incidentally, have persisted in the same patients for many months or years. The increased sensitiveness does not seem to depend upon the existence of a demonstrable infection or upon the carrier state. Of the 22 test subjects who had tonsillitis, 95 per cent gave a ++++ reaction. The authors discuss their findings rather fully and conclude that the positive skin reaction is regarded as an evidence of allergy to the hemolytic streptococcus or the product of its growth. The preponderance of strongly positive reactions in the nephritis group indicates that these patients may be highly allergic to the hemolytic streptococcus. The authors suggest that the development of an acute diffuse glomerular nephritis in patients suffering from a hemolytic streptococcus infection may be referable to the products of the growth of the hemolytic streptococcus acting upon previously sensitized kidney cells.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
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Pain Sensibility.—CROHN (*Am. J. Surg.*, 1929, 7, 474) states that it has been observed that the constitutional variation in pain sensitiveness alters the clinical history of gastric cases both functional and organic. Not only are the clinical history and the subjective symptoms modified by the degree to which the patient feels pain, but the very course is altered; favorably in those that possess the natural defensive mechanism of pain sensibility and unfavorably for those who by their constitutional deficiency fail to be conscious of so important a protective phenomenon. The hypersensitive individual comes early for treatment and begs relief. The insensitive person is relatively unconscious of his affliction and appears only when a major complication makes it impossible longer to deny the existence of a morbid process.

Correlations of Internal and External Pancreatic Secretions.—(DETAKATS (*Arch. Surg.*, 1929, 19, 775) says that the splenic portion of the pancreas was isolated from the rest of the gland in 25 dogs. The division with an electric cautery followed by wrapping omentum around the tail seemed the most satisfactory procedure. Specimens were taken from the isolated tail at intervals of from two days to one year. After a short period of edema a gradual destruction of the acinar elements takes place. There is an increasing amount of connective tissue which finally results in pancreatic cirrhosis. The ducts are first dilated, then show proliferation and infolding of their epithelium. Occasionally buds of epithelium form, resembling an early stage of embryonic development. The islands show edema for the first two weeks. Later there appear large solid cell complexes showing the vascular arrangement and staining properties of islet tissue.

THERAPEUTICS

UNDER THE CHARGE OF

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On the Chemistry, Pharmacology and Clinical Actions of Acedicon.—

I. The chemistry of Acedicon, which is a shorter name for Acetyl demethylo-dihydrothebain, is discussed briefly by SCHÖPF (*Deutsch. med. Wchnschr.*, 1929, 55, 302). The substance is closely related to morphin, being an isomer of acetyl codein.

II. WIELAND and BEHRENS (*ibid.*) present a brief summary of the pharmacologic actions of this new compound. They show that, while it is related to the opium alkaloids in many of its actions, it differs from them in a number of details. It does not produce habituation in dogs in the sense that there is no need for increasing the dose to produce a given effect when administration is continued over a long period of time. There are also no withdrawal symptoms. In point of activity on animals it lies midway between codein and thebain, being less toxic than the former. Its actions are exerted chiefly on the central nervous system. The respiratory center is depressed without any of the codein-like stimulation. There is no direct action on the blood pressure, blood-vessels or the heart, except that the latter is somewhat slowed as a result of the central vagus stimulation. It is markedly analgesic, resembling morphin in this respect.

III. Clinical study by NONNENBRUCH and RISCHAWY (*ibid.*) shows that the average single dose is about 10 mg., although larger single doses may be given for severe pain. The daily dose for oral administration to produce satisfactory analgesia or sleep may be as great as 30 to 50 mg. or more. These same doses administered subcutaneously produce similar analgesia and hypnosis in a shorter-time (about fifteen minutes) and in greater intensity than when administered by mouth. No observable harmful effects are produced upon respiration or upon the circulation. The drug greatly diminishes the cough reflexes but, unlike morphin, does not seem to check expectoration. Comparing it with morphin, the authors find that a subcutaneous dose of 10 mg. has about the same analgesic action as the same dose of morphin; about half the hypnotic action and about the same depressant action on the cough reflexes. The constipating action on the intestine is very much less than that of morphin. In comparison with codein, acedicon is about four times as active in suppressing cough and it is incomparably more active in analgesic and hypnotic action. So far as observations go there has been no suggestion of habituation in man and, inasmuch as the drug does not produce morphin-like euphoria, a craving for it does not seem likely.

The Action of Lobelin and of CO₂ on Respiration in Narcosis.—FRANKEN (*Klin. Wchnschr.*, 1929, 8, 439) reports careful and detailed comparative studies of the respiratory stimulation produced in anesthetized man by intramuscular and intravenous doses of lobelin and by the inhalation of 5 per cent CO₂ mixtures. He finds that the intramuscular use of lobelin in the ordinary dose of 10 mg. is relatively inactive in the presence of anesthesia, either by ether, chloroform, avertin or pernokton, all patients having been previously prepared by the administration of narcophin-scopolamin. In many instances, there is virtually no respiratory stimulation from this dose of lobelin. Intravenous administration of doses ranging from 1.5 up to 6 mg. produce marked increase in respiratory rate and volume, but these effects last only one to five minutes. Doses as small as 3 mg. given intravenously also produce some stimulation of the abdominal vagus. While lobelin rouses the patient rapidly from his narcosis, this cannot properly be ascribed to its respiratory effect since its action is too brief to account for adequate exhalation of the narcotic. The action of CO₂ mixtures is incomparably more intense and more effective than is that of any practical safe dose of lobelin and this combination of CO₂ with oxygen or air is absolutely without danger, which is not true of lobelin.

Injections with Harmin in the Treatment of Metencephalitis.—Following Beringer's reports of the actions of the alkaloid banisterin on the extrapyramidal motor system, RUSTIGE (*Deutsch. Med. Wchnschr.*, 1929, 55, 613) made clinical observations using the chemically identical alkaloid, harmin. He found no influence upon the circulation other than a variable slight effect upon the heart rate. Dizziness, tinnitus and a sense of drunkenness with occasional nausea appeared about fifteen minutes after injection of the drug and varied widely in intensity in different patients apparently without relation to the size of the dose. There was a prompt and very marked diminution in the muscular rigor which, in some patients, amounted almost to complete disappearance. This effect, however, lasted only from a few minutes to a very few hours. Tremor was sometimes temporarily increased but in most instances was diminished or checked for a short period of time. Voluntary movements were markedly improved both in their completeness and the rapidity with which they were carried out. The improvement in this respect appeared in some ten or twenty minutes but had disappeared in all cases within an hour after the dose. In all respects these results were similar to those obtained with banisterin. From the foregoing well controlled observations Rustige concludes that neither harmin nor banisterin is of any important therapeutic value and that neither one offers any prospect of becoming so unless some means be obtained by which their actions can be sufficiently prolonged to make them of clinical value.

Clinical Investigations on the Localization of Action of the Analgesics.—Pointing out that our knowledge as to the precise portions of the brain upon which the local analgesics exert their action is fragmentary, HOFF and WERNER (*Klin. Wchnschr.*, 1929, 8, 488) report a series of careful investigations carried out in man. Their subjects included normal patients and patients proved to have organic lesions of the optic thala-

mus. As a criterion of the analgesic action they employed the Martin-Macht method of electrical determination of skin sensibility. They find that such representative analgesics as atophanyl and pyramidon produce uniform bilateral analgesia in normal persons and in those suffering with a considerable variety of nervous diseases. In five patients with extensive thalamic lesions analgesia was found to be produced only upon the side of the body on which the thalamus was normal, skin sensibility being unchanged on the diseased side. On the contrary, morphin produces equal bilateral analgesia in these thalamic cases just as in normal individuals. From these observations the authors conclude that the seat of action of the analgesics such as atophanyl and pyramidon lies in the optic thalamus. Following upon this conclusion it is interesting to note that, through the administration of atophanyl and the discovery of its site action, the authors were able to make a correct diagnosis of a thalamic lesion in a patient otherwise unsuspected.

PEDIATRICS

UNDER THE CHARGE OF

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The Prevention of Tuberculosis in Children.—CASPARIS (*J. Am. Med. Assn.*, 1929, 93, 1639) advocates tuberculin tests on all school children as a part of a plan for the prevention and control of the disease. In children with positive reactions, the pre-school children of the family should be tested. Investigation into the histories of the adult members of the family should be made and those with suggestive symptoms should be examined carefully in an attempt to find the source of dissemination. This process of finding tuberculosis in all its various stages should be the function of health organizations. The next step would be the distribution of the care of all of these individuals. He feels that success in the prevention of tuberculosis will require the aid of the practising physician who is really the ultimate health officer. Records of the positive tuberculin test, the state of the child's nutrition, including height, weight and age, and of the condition of the tonsils and teeth should be made. This record along with any other available data, such as recommendations for care, should be sent to the family physician. In the same way adults in whom the disease is suspected should be sent to the family physician or if they cannot afford a private physician to some dispensary. The author realizes that the carrying out of such a plan as this would be a tremendous task but he feels that as tuberculosis is a tremendous problem, in spite of the large work it should be attempted and widespread coöperation secured. In order to accomplish this, years of organization may be required. Educational propaganda must be used in schools and in clinics and meetings with physicians and the laity. The tuberculin test is of the greatest importance.

Cereals and Rickets.—STEENBOCK, RIISING, BLACK and THOMAS (*J. Am. Med. Assn.*, 1929, 93, 1868) made antirachitic active various cereal products such as whole-wheat meal, patent white flour, shredded wheat biscuit, cream of wheat, whole-corn meal, corn flakes, hominy and rolled oats by irradiation with ultraviolet rays. They found that this activity was stable to autoclaving for thirty minutes at 15-pound pressure followed by drying at 60° C. for a few days. Storage for sixteen months at 60° C. or at lower temperature did not cause destruction but after from twenty-three to twenty-eight months there was a decrease in potency. Even untreated cereals kept shorter periods than this became too unpalatable for human use. Household cooking did not have any effect on the antirachitic activity. Vitamin A and the vitamin B complex are labile to ultraviolet radiation but evidence of their destruction in cereals cannot be obtained with such an exposure as is necessary to secure the best antirachitic activation. The commercial irradiation of cereals has been standardized so that the activity induced did not exceed by a multiple of 3 that necessary to form bone of the best ash content. In this way there was prevented any change in palatability, destruction of vitamins and danger of hypervitaminosis. By feeding commercially irradiated rolled oats, rickets was prevented in dogs and rats and no interference in growth of reproduction was shown in the latter over a duration of fifteen months in four generations.

The Early Diagnosis of Appendicitis in Children.—FLUSSER (*München med. Wchnschr.*, 1929, 76, 1542) states that in children who are operated on for acute appendicitis it may sometimes be seen that the appendix show the signs not only of an acute appendicitis but also of chronic inflammation and adhesions. Such conditions indicate that the child had suffered previously from appendicitis, but that the condition had not been recognized. In order to detect signs which at the times of the first attack of appendicitis had not been recognized as indications of the disease the author studied the past history of such patients. He found that aversion to eating and loss of appetite were always present. He found as another frequent sign, rectal tenesmus. This was manifested in a desire for defecation but no result following the straining. Vomiting may also be a sign of appendicitis. Limping on the right leg without any evidence of bone or joint disease is suggestive of appendiceal inflammation. The frequent or suppressed urination and the desire to urinate without the passing of urine is almost always a sure sign of appendicitis. One of the difficulties encountered is the difficulty of localizing abdominal pain in children. Abdominal rigidity may not be recognized because of crying. The differential diagnosis is especially difficult in cases of inflammation and other infectious diseases. Umbilical colic often simulates appendicitis.

The Relation Between Colic and Eczema in Early Infancy.—WHITE (*Am. J. Dis. Child.*, 1929, 38, 935) states that very young infants with true colic or vagogenic gastroenterospasm, in whom eczema develops later are almost three times more numerous than those suffering with either condition alone. Allergic family history is found with about the same frequency in infants with eczema with colic, or with both. The usual sequence is first colic, then diarrhea, followed by vomiting occur-

ring from two to four weeks of age and finally eczema appearing about ten weeks of age. Atropin is effective about three times more frequently in infants with colic alone than in infants with both colic and eczema. In some cases of colic in which atropin produces no improvement, the feeding of thick cereal may be beneficial, but there is no evidence that the feeding of thick cereal predisposes the eczema. Because of hyperacidity that is associated with hypomotility infants with gastroenterospasm seem to tolerate sweet milk better than lactic acid milk. The author believes that exudative diathesis, vagotonia and vagogenic gastroenterospasm with or without eczema are of a common allergic basis.

Interpretation of Roentgenograms of the Chest in Children Based on Observations at Necropsy.—BIGLER *Am. (J. Dis. Child., 1929, 38, 978)* studied the lungs of 171 children coming to necropsy to determine what pathologic changes were present to account for the shadows seen in the roentgenograms of the chest. He feels that it is impossible to formulate any standard for a normal chest for the Roentgen ray standpoint and the interpretation of Roentgen ray pictures should go hand in hand with the history, clinical and physical observations and laboratory data. The hilum shadows and the linear markings are made up for the most part of the blood in the bloodvessels and not of the bronchi. The rounded shadows of even density occurring in the inner third of the lung fields as well as those found along the linear markings are due to bloodvessels running parallel to the actual axilray. Normal lymph glands do not cause shadows. Hypoplastic lymph glands whether caseated or inflammatory, whether in the hilum or intrapulmonary tissue, cannot be recognized as such if they do not contain calcium. They will not cast shadows unless they are large enough to encroach on the pulmonary fields from the mediastinum or from the hilum, or unless they are visible by contrast in the air-filled pulmonary tissue. The size and shape of the shadows at the hilum is influenced not only by active infection but also by the remains of previous infections.

Early Rheumatic Infections of Childhood.—MCLEAN (*Arch. Pediat., 1929, 46, 657*) studied 118 patients with early rheumatic infections. Of these 67 were girls and 51 were boys. The largest number of cases was seen between the sixth and seventh years. Histories of repeated attacks of tonsillitis with nasopharyngeal infections were noted in 89 or 75 per cent of the cases. Pains in the legs, joints or stiffness of the limbs was observed in 80 or 60 per cent of the cases. Clinical symptoms or physical signs of a mild chorea were seen in 42 cases of which 27 cases were girls and 15 boys. Soft blowing systolic heart murmurs were heard in 84 or 71 per cent of the cases. Underweight for the height was noted in 103 or 87.3 per cent of the cases whereas underweight for age was noted in 92 or 77.9 per cent of the cases. Of this group of patients 35 developed clinical symptoms and physical signs of rheumatic infection while under observation. The tonsils were considered the foci of infection in 57 cases and 54 or 97.7 per cent of this number had heart murmurs and 7 or 12.2 per cent had evidence of chorea. In 9 children in whom both the tonsils and the teeth were considered the foci of infection, heart murmurs were heard in 6 and there were physical signs and

symptoms of chorea in 6. In 16 cases in which the teeth alone were thought to be the foci of infection there were only 4 patients with heart murmurs, all of whom had had the tonsils removed previously and gave histories of having had repeated attacks of tonsillitis.

Tonsillectomy in Prevention and Treatment of Rheumatism.—FINDLAY, MACFARLANE and STEVENSON (*Arch. Dis. Child.*, London, 1929, 4, 313) feel that a preliminary tonsillectomy may possibly render and individual susceptible to rheumatic infection but not to chorea. A preliminary tonsillectomy or one performed early during the course of infection may in the case of arthritis render the heart less liable to be attacked but this does not hold true of chorea. As cardiac complications usually develop during the first or second rheumatic attack, the operation, in order to prevent cardiac injury, should be performed prior to a possible second attack. Tonsillectomy in the case of carditis following arthritis seems to have a beneficial effect on the progress of the disease, but this does not hold true in carditis following chorea. The varying behavior in response to tonsillectomy of examples of the rheumatic infection characterized by chorea and by arthritis suggests the possibility of a different strain of the infective organism in these two types of the disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Previous Treatment of Patients who Have Developed Neurosyphilis.—WEATHERBY (*Am. J. Syph.*, 1929, 13, 339) takes as his thesis the moot question of influence of specific treatment in syphilis on the incidence of neurosyphilis. His study embraces 280 cases, of which 135 were paresis, 37 were psychoses with cerebral syphilis, 31 tabes dorsalis and 77 cerebrospinal syphilis. Of the paretics, only 16 were definitely known to have had previous treatment and but 2 of these received prompt and adequate arsphenamin therapy. The author concludes that paresis occurs independently of treatment with arsphenamin, and that paresis usually develops in the undiagnosed, the neglected and inadequately treated patients. The author drew no conclusions from his group of psychoses and tabes dorsalis in which there were histories of treatment in 19 per cent and 22.6 per cent. Of the 77 patients with cerebrospinal syphilis, definite knowledge of treatment was recorded in 19 or 25 per cent. The author believes that in this series arsphenamin appeared to predispose to the early onset of cerebrospinal syphilis and points out that neurologic symptoms appeared on an average in less than three years after the primary lesion in the treated cases, while the

symptoms were delayed in the untreated cases to ten years. (The reviewers dissent with the writer on these conclusions and differ with him in his conception of adequate treatment. By generally accepted modern standards, but few, if any, of his patients received adequate early treatment. In the 2 cases receiving the maximum number of arsphenamin doses, no note is made of the additional use of mercury or bismuth. The reviewers feel that the maxim "A little treatment may be dangerous" is illustrated and it is rather the lack of *sufficient* arsphenamin rather than the *use* of arsphenamin that constitutes the etiologic factor.)

Retention of Bismuth in the Organism in the Treatment of Syphilis.—LOMHOLT (*Arch. Derm. and Syph.*, 1929, 19, 891) reviews the literature on the absorption and excretion of bismuth salts by the experimental animal. Intramuscular deposits of bismuth, particularly compounds of low solubility and "oil suspension" are excreted rather slowly by the body. Absorption is determined by two main factors, the chemical formula of the salt and the fineness of the suspended particles in the compounds. Saturation of the tissues with bismuth is of some therapeutic importance; not only because of its effect on the spirochete, but also because of the continuance of this saturation makes it possible to maintain a certain antisyphilitic effect for some time after the cessation of treatment. Most of the reports on direct investigation deal only with storage in the viscera and the quantities are not large although they have the highest concentration of the metal. The occasional investigations on the supporting tissues have revealed rather small concentrations. The total amount of bismuth found in the tissues and organs is but a small fraction of the total quantity injected. Gruhzt, Tendick and Sultzaberger hold a different opinion and believe that for a long period after treatment large quantities are diffused and stored in the tissues. They arrived at this conclusion after determinations on the excretion through urine and feces together with determinations on the excised deposit mass. Later these authors concluded that bismuth is practically fixed in the bone which serves as a storage depot. Lomholt, by a special radiochemical method, using bismuth oxychlorid in both water and oil and working with guinea pigs, determined the amount of bismuth in: (1) The site of injection; (2) the viscera and specimens of the muscular and bone tissue; (3) the rest of the body; (4) the daily excretion of urine and feces. The rate of absorption varied greatly; in 5 cases more than 50 per cent was absorbed after ten days. Small injections seem to be absorbed relatively more quickly than larger ones. The major part of the quantity injected was excreted relatively quickly with the urine and feces. Another large although varying amount remained at the site of injection. Only small quantities were diffused and stored in the tissues making up the "true retention." From seven to ten days later only 4.7 per cent to 13.1 per cent was left. The majority of the retained bismuth was deposited in the abdominal viscera, especially the kidneys, liver and large intestine. The author could not confirm the observation that bone acted as a storage depot. Although weak concentrations, about 1 per cent, were used in this work, and in human therapy concentrations weaker than 5 per cent are not feasible, the author concludes in general that the rate of elimination corresponds well with that of absorption.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Roentgen Therapy of Fibromyomata.—In the course of her twelve years' experience with the Roentgen treatment of uterine fibromyomata HANKS (*Radiology*, 1929, 12, 403) has found that there are a few questions which are asked so frequently by not only the laity but also by physicians that she answers them categorically: (1) If the tumor is not treated surgically, is there greater danger of cancer? She believes that Roentgen ray is a safeguard against cancer but certainly such women are not more prone to cancer than normal women. (2) Does Roentgen ray therapy injure a woman sexually? She has taken great pains to ascertain the truth on this apparently urgent question. Many of her patients state that since being relieved by Roentgen ray therapy, intercourse has been resumed normally because of absence of pain and the fear of conception. The knowledge that the pelvic organs are intact also helps. It is safe to say therefore, that Roentgen radiation in small doses, not frequently repeated and not continued too long, does not affect sexuality. (3) Will a woman become obese? If the woman is naturally obese, she will probably remain so, and after the menopause she may gain weight, as women did before the Roentgen ray was discovered, but under conservative application of Roentgen radiation she is no worse than she would have been without it. (4) The questions prompted by the perennial fear of burns from the Roentgen ray are many. The fact that she has had no burns nor other accidents in more than twelve years, proves that they can be eliminated.

Roentgen Therapy of Uterine Fibroids.—In presenting his experiences with the Roentgen irradiation of fibroid tumors of the uterus, LINDENBERG (*California and Western Med.*, 1929, 31, 93) states that the effect of the rays in this condition is due to their effect on the ovaries, namely the production of castration. When considering this type of treatment there are certain contraindications which must be borne in mind. Younger women in whom we wish to preserve ovarian function should not be irradiated. Such patients show better results from myomectomy or hysterectomy. Surgical interference in which the ovaries can be preserved is a lesser insult than a premature menopause with its intense disturbances. Women who wish to have children should also be excluded from radiation therapy. Very nervous women are more benefited by operation with preservation of the ovarian function because in such patients the sudden exclusion of the ovarian hormone often aggravates the unbalanced nervous system. In dealing

with any abdominal tumor difficulties are often encountered in ascertaining the correct diagnosis. There is scarcely a more dangerous agent in the whole field of medical therapy than Roentgen rays if improperly applied. It is very important therefore that the supposed fibroid is not in reality a pregnant uterus, an ovarian tumor or a pyosalpinx. There are also certain types of fibroids which must be excluded. When the tumor is undergoing degeneration it should be removed in order to eliminate the danger of sepsis or peritonitis. In the presence of submucous tumors the bleeding is caused not only by the ovarian influence, but also mechanically by an erosion of the overstretched thin-walled veins in the endometrium. Radiation of such tumors is not only unsuccessful but if the tumor is big and an intensive dose is applied the life of the patient is at times endangered because the irradiation causes an involution of the uterus and an obliteration of the blood supply and possibly a necrosis of the tumor. Large tumors and those causing pressure symptoms should not be irradiated as it will take much too long to obtain the desired effect. Malignant degenerations should usually be excluded from this type of treatment as surgery gives much better results. In brief therefore, those tumors are suitable for Roentgen therapy which are correctly diagnosed uncomplicated fibroids with menorrhagic disturbances. Such tumors are usually of the interstitial variety and will constitute about 25 per cent of all fibroids. As an example of the care which he has exercised in his work it may be stated that he has irradiated 59 patients and refused treatment to 44 in whom he deemed the treatment unsuitable. In 30 per cent of the patients treated the fibroid totally disappeared, in 39 per cent the tumors shrank to less than half their former size and in 11 patients the tumors shrank to about one-third the original size. In about 5 per cent there was no shrinkage of the tumor but amenorrhea was produced with complete relief of symptoms. He believes that if the diagnosis is correct and the cases are properly selected success may be expected in 100 per cent of the cases with no untoward results. In our clinic, where radium is always available, we seldom resort to Roentgen therapy. We believe that the majority of tumors should be treated by surgery, a minority of properly selected cases may be satisfactorily irradiated with radium, while we reserve Roentgen irradiation for those patients who are not fit subjects for surgery on account of constitutional contraindications and whose tumors are too large for radium therapy a diagnostic curettage should precede irradiation by either radium or Roentgen ray.

Vaginal Metastases of Fundal Cancer.—Vaginal metastases which accompany cancer of the uterine fundus have been the object of a study carried on by MEIGS (*New England J. Med.*, 1929, 201, 155). He found that this condition is not an uncommon lesion since 12 per cent of all cases of fundal adenocarcinoma seen at the Collis P. Huntington Memorial Hospital had such metastasis. Cancer in the vagina should not be regarded as primary there until the uterus has been investigated. These metastases probably take place by way of the lymphatics or possibly by venous channels, while direct implantation is less probable. Hysterectomy is to be preferred when the vaginal metastasis seems treatable and the uterine tumor operable. Radium should be used in the uterine canal and in the metastasis if either the original tumor or the

local metastasis is inoperable or untreatable. Infiltration of the metastasis with gold or glass seeds and a surface application with about 2500 millicurie hours of lead screened radiation is the treatment preferred in dealing with the local vaginal metastasis. In 10 out of 16 cases so treated in this series the growth disappeared while in 6 cases the growth was not favorably influenced. Four proven cases out of 24 who had adenocarcinoma of the fundus with metastatic nodules of carcinoma in the vagina are alive and well nine years, seven years, five years and seven months respectively after treatment. This study indicates the necessity of careful periodic vaginal examination following either hysterectomy or radium treatment of fundal cancer.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Herpes Zoster Ophthalmicus Apparently due to Chronic Frontal Sinusitis.—Herpes zoster ophthalmicus following upon chronic frontal sinusitis appears to be rare. LANDIS (*Penn. Med. J.*, 1929, 32, 765) reports the case of a man in which the right forehead and region of the right eye was involved. Examination elicited tenderness over the frontal bone and above the internal canthus. The mucous membrane of the nose was greatly congested with enlargements of both middle and inferior turbinates. On the right side there were several polyps and pus was present in the middle nasal passage. The pharynx and tonsils were also congested. The right eyelid was edematous and the conjunctiva very congested. The cornea was not involved. The pupils reacted to light and accommodation, but the left pupil was slightly larger than the right. The retina was normal except for a slight overfilling of the veins. The left eye was normal. A radical operation was done by the Lathrop method, pus evacuated, hyperplastic tissue removed and a drainage tube passed through the nose. The patient improved and the herpetic condition began to dry up on the second day. Two weeks later since pain persisted though the herpetic condition had cleared up the ethmoid cells and the bulla were partially removed together with the anterior tip of the middle turbinate. Some pain and burning still persisted after dismissal; this was probably due to a nerve caught in the scar. It improved under diathermy. Because of the localized nature of the eruption Landis attributed it to peripheral reflex irritation of the supraorbital branch of the superior division of the fifth nerve from chronic frontal sinusitis.

Appearance of Peculiar Petechiæ in the Conjunctiva in Endocarditis Lenta.—Petechiæ with a white center on the conjunctiva have been considered an accidental occurrence in endocarditis lenta. OETTINGER

(*München. med. Wchnschr.*, 1929, 76, 796), however, investigating them, found that they occurred with extraordinary frequency. They are of varying size, round or spindle-shaped and dark red, more often located on the conjunctiva of the lower than of the upper lid and most frequently on the transitional fold. The white center is really gray-white, is sometimes placed peripherally and sometimes so small as to be visible only with the loupe. Only rarely is it absent. The individual petechia lasts for a few days, gradually paling. For sometimes thereafter a yellowish brown fleck remains. Histologic examination showed that the petechia consisted of hemorrhage with cellular infiltrate (white center). During the past two years in which Oettinger has been looking for these petechiæ they have never been absent from a case (14). They show a periodic appearance and disappearance, not being present at every examination. More often they appear during an exacerbation, but are sometimes found at the beginning of the disease. In 2 cases petechial hemorrhages in the skin and buccal mucosa also appeared shortly before death. In the other 12 cases (6 substantiated at autopsy) the petechial formation was limited to the conjunctiva. Since these hemorrhages often occur in the early stages of the disease and the cutaneous ones do not appear any too frequently and when present usually do not appear until the end stages of the disease, the conjunctival hemorrhages may serve to decide the diagnosis in doubtful cases.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Experimental Herpetic Encephalitis in the Guinea Pig Produced Through the Respiratory Tract.—Having produced herpetic encephalitis experimentally by feeding herpes virus to guinea pigs, MCKINLEY (*Proc. Soc. Exper. Biol. and Med.*, 1929, 26, 699) considered the possibility of infecting guinea pigs by dropping herpetic brain emulsion into the nostrils of these animals. His experiments indicated that, in certain cases, the virus of herpes may reach the brain of guinea pigs following deposition of the virus in their nares. That only a few animals so inoculated became infected is considered by the author to be significant of the fact that even highly virulent strains become attenuated by passage through guinea pigs by the feeding and inhalation methods employed. While practically nothing is known concerning the portal of entry of the true virus of epidemic encephalitis in man, and while there is little evidence to support the view that epidemic encephalitis is caused by the herpes virus, the possibility of infection by such a virus through the respiratory tract may prove to be of importance from the epidemiologic point of view.

Lesions in Nasal Mucous Membranes of Monkeys with Acute Poliomyelitis.—The ease with which monkeys may be infected with poliomyelitis by nasal instillations of virus either with or without preliminary scarifications of the nasal mucosa has been known since the early experiments of Flexner and Lewis. In view of the fact that virus has been demonstrated in the nasal secretions of human "carriers," STEWART and RHOADS (*Proc. Soc. Exper. Biol. and Med.*, 1929, 26, 664) examined histologically the nasal mucosæ of monkeys dying of acute poliomyelitis to ascertain if any demonstrable changes were evident. No lesions suggestive of any specific character were seen in the deeper structures of the nose. However, in 17 of the 31 monkeys with experimental poliomyelitis, interesting lesions, consisting of isolated necroses of the epithelial cells of the respiratory (nasal) mucosa were encountered; along with an acidophilic degeneration of the nuclear chromatin, leading to an appearance strongly suggesting inclusion bodies—the nature of which is uncertain. The authors are of the opinion that further study is required to determine whether these intranuclear acidophilic bodies are inclusions in a specific sense.

Further Consideration of Transmissibility of Human Upper Respiratory Infections (Common Cold) to the Ape.—SHIBLEY, MILLS and DOCHEZ (*Proc. Soc. Exp. Biol. and Med.*, 1929, 27, 59) some time ago reported upon the suitability of the anthropoid ape as an experimental animal for study of the common cold, because of the fact that the upper respiratory flora of these animals resembles closely that of humans, and these animals are very susceptible to colds when exposed to human beings suffering from such infections. They showed that nasal washings obtained from humans suffering with typical colds produced the same symptoms in the apes when injected intranasally. They now discuss the importance of control experiments which would not be adequate unless they were carried out in a period of the year when ordinary colds were at a minimum, because of the possibility during the months in which colds are present of using filtered nasal washings from individuals apparently well, but who might be carriers of the active agent. These control experiments consisted of a repetition of the transmission experiments of the previous winter, using nasal washings in healthy individuals who had had no colds for at least three months and who were not exposed to colds during that time. Control experiments gave absolutely negative results and were seen to prove definitely that the earlier transmission experiments were definitely positive, indicating that the type of upper respiratory infection under consideration is caused by filtrable virus.

Studies in Asthma. IV. The Nose and Throat in Asthma.—With the idea of finding the part played by focal infections and other disturbances of the nose, throat and teeth in asthma of all kinds, RACKEMANN and TOBEY (*Arch. Otolaryngol.*, 1929, 9, 612) reviewed the data of 1074 asthmatics—28 per cent of whom had had operations on the nose and throat without regard to the cause of asthma as found. A true focus of infection in the nose, throat and teeth was encountered in 44 per cent of all cases, while vasomotor rhinitis occurred in 14 per cent. As one would expect, there were more patients with an infective focus in the *intrinsic*

than in the *extrinsic* group. It was learned that the presence of these foci have little relation to the outcome of the asthma. After outlining the treatment of these various foci, the authors observed that the gross results of this treatment were disappointing, as shown by the comparison of patients with foci in each group on whom operations were and were not performed, and by analysis of the different lesions treated; and that local treatment of the nose, throat and teeth apparently had afforded permanent relief from asthma in 5 per cent of cases. The absence of demonstrable infection in the contents of "infected" sinuses in two instances suggested that local lesions of the nose and throat may develop from the same fundamental cause as the asthma itself and be part of the pathologic process of the disease.

The Pathogenesis of Cholesteatoma.—Suppurations of the middle ear are the commonest conditions encountered by the otologist; and the most important of these are the chronic types associated with the formation of cholesteatoma. It is recognized that cholesteatoma begins as an epidermization of the lining of the cavity of the middle ear and may take place by one of several different methods. As a rule the epidermization occurs following the destruction of the normal middle-ear mucosa and tympanic membrane, seen so frequently after an acute exanthematous otitis media or a chronic process such as tuberculosis of the middle ear. In either event it has been accepted generally that a relatively long period elapses between the initial suppuration and the formation of cholesteatoma. In reporting the clinical and microscopical findings of a case of fulminating scarlet fever, with spontaneous rupture of the tympanic membrane on the sixth day and death from septicemia a week later, POLVOGT (*Arch. Otolaryngol.*, 1929, 9, 597) found a distinct ingrowth of squamous epithelium from the external auditory canal with a beginning cholesteatoma of the tympanic cavity. He states that this is the earliest known formation of this growth (seven days after a spontaneous marginal perforation from an acute necrotic scarlatinal otitis). In the light of these pathologic findings, the author emphasizes the advisability of performing a radical operation in both the acute and chronic (usually tuberculous) forms showing cholesteatomous formation.

Agranulocytic Angina. A Report of Three Cases with Necropsies.—In 1922, Schultz described a series of cases of gangrenous stomatitis associated with a marked leukopenia affecting chiefly the granular leukocytes. Since then many similar instances have appeared in the literature of this country and abroad, so that in 1928, Hueper was able to collect about 125 recorded cases. While agranulocytic angina is the term most commonly applied to this condition, some prefer the name *agranulocytosis*, and Hueper referred to it as *agranulocytosis* (Schultz). In presenting the clinical and necropsical data of 3 cases (in one of which the authors were not entirely convinced of its agranulocytic anginal character), THOMAS and SERVICE (*Clifton Springs Med. Bull.*, 1929, 15, 219) were able to confirm many of the outstanding features of the disease, namely, the gangrenous stomatitis, the grave leukopenia (often as low as 1000 and sometimes nearer 100 white cells per c.mm.), the paucity or absence of granular leukocytes, the diminution of polymorphonuclear leukocytes in the exudate in the bronchopneumonia,

and the total absence of cells of the myelocyte series in the bone marrow. The onset of agranulocytosis is usually sudden, being ushered in by sore throat and fever. The course of the malady is rapidly progressive, the patients becoming extremely ill and septic. Coma ensues early and death often takes place in five to ten days. Many different types of microorganisms have been isolated, but no one organism, or group of organisms, have been found to be constantly present. It is inferred from these facts that the breaking down of the bodily resistance, due in part to the loss of polymorphonuclear leukocytes, permits bacteria to invade the tissues. In other words, the specific cause of agranulocytic angina is unknown at the present time.

RADIOLOGY

UNDER THE CHARGE OF

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Intrapelvic Protrusion of the Acetabulum.—Eight cases of inward protrusion of the acetabulum are reviewed by DOUB (*Radiology*, 1929, 12, 369). The condition is rare, though first described more than a hundred years ago. Its cause has not been ascertained, and several factors are probably concerned. Osteoarthritis is a common accompaniment, and this may be a late stage of some general disease in early life causing softening of the bones with the resultant deformity. Clinical findings refer mostly to pain and restriction of normal motion of the hip. The Roentgen picture discloses a deepening of the acetabulum with thinning of the mesial and inferior wall and bulging of the acetabulum into the pelvis. The head of the femur is therefore more deeply buried, and the greater trochanter is somewhat higher and closer to the acetabulum.

A Roentgenologic Consideration of Duodenitis.—In 1921, Judd directed attention to duodenitis, a diffuse inflammation of the duodenum, with or without actual ulceration. His observations have been confirmed from the histopathologic standpoint by MacCarty, Konjetzny and Wellbrock. KIRKLIN (*Radiology*, 1929, 12, 377) reviews the findings in 45 cases observed recently at the Mayo Clinic. This series indicates that duodenitis is characterized roentgenologically by marked irritability of the bulb, which tends to empty itself quickly but not completely. It is best recognized during the period of emptying; the bulb does not empty in a normal even manner, but a spastic, grossly-deformed, skeleton-like cap is seen, although it may appear normal

during the filling phase and while full. The deformity differs from that of typical ulcer in that its borders are less sharply defined, no marginal or central niche can be seen, and there is no gastric retention. Its positive distinction from frank ulcer is not yet feasible, and it might be confounded with reflex spasm of the bulb, but it seems to warrant further study.

Endothelial Myeloma.—Nine cases of endothelial myeloma are reviewed by KIRKLIN and WEBER (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 355). The oldest patient was twenty-nine, the youngest patient two and a half years; the average being eleven years. All the patients except one were males, and they were mostly of asthenic build. Bones involved were: the femur in 4 cases, fibula in 2, tibia in 1, humerus in 1 and scapula in 1. In the long bones the disease seemed to prefer the upper portion of the shaft. Roentgenologically it is characterized early by a translucent area, corresponding to the tumor, in the medulla; the tumor enlarges, expands and destroys the cortex and invades the soft tissues. A striking feature in the cases here reported was a fine-meshed gauze-like shadow in the invaded soft tissues, due apparently to an effort at periosteal repair. Osteomyelitis and osteosarcoma may enter into the differential diagnosis.

Early Diagnosis of Perforated Peptic Ulcer.—A case of perforated ulcer near the pylorus is reported by GEIER (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 465) in which free intraperitoneal air was demonstrated with the Roentgen ray within ten minutes after the perforation occurred. The air was visible as a rarefied space between the dome of the liver and the under surface of the diaphragm, also between the diaphragm and the abdominal viscera on the left side. In every case of perforation of the stomach or duodenum free gas and fluid are present in the peritoneal cavity. Search for this evidence with the Roentgen ray should not require more than five minutes, since the patient can be placed before the roentgenoscope while still on the hospital carriage, and no special preparation or contrast meal is necessary.

Indications for Radiation Therapy in Benign Uterine Hemorrhage.—The prime indication for radiation therapy in benign diseases of the uterus according to SCHMITZ (*Am. J. Roent. and Rad. Therap.*, 1929, 21, 327) is hemorrhage, but this is subject to qualifications. Infections, displacements, traumas, and accidents of pregnancy call for either medical or surgical treatment. The necessity of a correct diagnosis before treatment is begun is emphasized, and in all doubtful cases immediate diagnostic curettage or excision of suspected areas of tissue for microscopic examination is imperative to rule out malignancy. No treatment is required in myomas not causing symptoms. Radium treatment is indicated in myomas causing hemorrhage: (a) if they are free from complicating infection, especially adnexitis; (b) if they are not associated with complicating pelvic diseases requiring surgery, such as ovarian tumors; (c) if they are not larger than a four-month pregnancy; (d) if they are not degenerating; (e) if they are not growing rapidly; (f) if they are located intramurally; (g) if they are not complicated with a severe anemia out of proportion to the symptoms and

clinical findings; (*h*) if they are not causing pressure symptoms; (*i*) if they occur in patients thirty-six years of age or older; (*j*) if they do not occur in persons with personal or familial neurotic tendencies; (*k*) if there is no doubt about the diagnosis. Less than 11 per cent of the cases of myomata in Schmitz's series were treated by irradiation, and the treatment of choice is surgery. The predominant method of treatment in hypermenorrhea due to atonicity and hypoplasia of the uterus was medical. The medical treatment consisted in the use of ergot, hydrastis, pituitary extract from the anterior lobe, adrenalin, regulation of food and exercise. If medical treatment failed then dilatation and curettage were employed, and if the latter failed irradiation was used. Contraindications to irradiation, however, are: (1) coexisting infections such as adnexitis and pelvic peritonitis; (2) patients under thirty-six years of age; (3) neuropathic tendencies.

Use and Abuse of Physical Therapy in Chronic Arthritis.—In the opinion of STONER and BROOKHART (*Arch. Phys. Ther., X-ray, Radium*, 1929, 10, 149) physical therapy should be used only as an adjunct and not independent of accepted general measures of treatment in the management of the chronic arthritic. This implies an accurate diagnosis and a rational classification of the various clinical manifestations of the disease. The authors admit that in a series of 140 cases of chronic arthritis, baths, massage, ultraviolet ray and diathermy were used with considerable disappointment in certain cases. In the whole group of chronic diseases, perhaps none are more difficult to treat than chronic arthritis; any or all forms of treatment yield unsatisfactory results at times. Diathermy, which occasionally seems to have value, more often is disappointing, and in the more acute cases seems to be contraindicated. In the treatment of this group of 140 cases, effort was made to improve the general health. A relatively low-carbohydrate was advised in most cases, and a low-caloric intake in the obese. Rest, avoidance of exercise and encouragement of elimination was the routine in all cases. Drug therapy comprised the salicylates, cinchophen, iodides, amido-oxylbenzoate, and in the obese with a low-metabolic rate thyroid extract was judiciously administered. Colonic irrigations were used as a routine. Marked improvement followed in 14 per cent, definite improvement in 61 per cent, no improvement in 8 per cent, and 10 per cent were questionable.

Physical Measures in the Treatment of Pain.—When the local production of pain is the result of a toxin carried to the part, there are two plans of treatment, according to BEHAN (*Arch. Phys. Therap., X-ray, Rad.*, 1929, 10, 390); one is to deaden receptivity of the nerve itself and the other is to remove the toxin. In the first method ice may be applied, in the second method heat. Throbbing pain in all inflammations, whether septic or otherwise, can be very definitely relieved by a Bier hyperemia bandage applied above the inflamed area. Pain produced by movement, as in joints, is relieved by immobilizing with splints. Painful scars can frequently, by the use of the Roentgen ray, be softened and then permanently eradicated by the use of the ultraviolet light and diathermy. The galvanic current is useful in cases of painful sphincter contraction, especially in cases of anal fissure. Overdilatation of the

anal sphincter, the vesical sphincter, or the os uteri, with or without anesthesia, is often of value in relieving painful conditions. Joint distention is a common cause of pain in certain varieties of arthritis; compression over the joint with a large dry bath sponge held in place by a bandage is often effective; the sponge may also be moistened with a saturated solution of magnesium sulphate. Hyperextension of the thigh sometimes relieves sciatica, and diathermy is beneficial. The Roentgen ray can be employed in many cases of terminal nerve pain due to toxemia, in reflex pain and in neuritis. The ether spray is useful in many cases of referred pain, especially pain associated with the cranial nerves.

Surgical Procedures in Carcinoma of the Rectum.—RANKIN (*Radiology*, 1929, 13, 207) notes that at the Mayo Clinic the cases of carcinoma of the rectum are arbitrarily divided into two distinct groups, the operable and the inoperable, the former being recommended for surgery, the latter for palliative operation, radium and Roentgen ray, or irradiation alone. The presence or absence of metastasis and the degree of malignancy as graded after Broders' method, affect the result from either procedure. In a large series of cases, when metastasis was present operation yielded good results in approximately 20 per cent only; when it was absent operation was effective in more than 57 per cent. The results obtained in cases in which malignancy was graded 1, with metastasis, were almost as good as in cases in which malignancy was graded 3 and 4, without metastasis. The average duration of life after operation decreased as the grade of malignancy increased. Grading of malignancy aids in the selection of cases for treatment by operation or radium or both. Malignant growths of grade 3 or 4 are more radio-sensitive than those graded 1 and 2.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Congenital Auditory Imperception (Congenital Word Deafness): With Report of a Case.—WORSTER-DROUGHT and ALLEN (*J. Neurol. and Psychopath.*, 1929, 9, 193) present a case in which a boy, aged twelve years, was unable to understand speech by auditory perception but who showed no evidence of deafness and was able to carry out commands by lip reading. The case was complicated to some extent by a certain degree of word blindness as well. There was no defect of

hearing and the muscles of articulation were intact. The peripheral organs of sight were also normal. The patient would often repeat words as he heard them and repeat them many times with no obvious appreciation of their meaning. It was also noticeable that he did not recognize mistakes in music that were very gross and was not disturbed by discords. He could not repeat correctly a number of musical notes sung in his hearing. On the evidence presented they conclude that there is a complete absence of memory for words and musical tones. The patient was unable to use words spontaneously until he had acquired the art of lip reading. The authors then branch into a discussion of "centers" for word memory and conclude, because of the development by the patient of a language of his own, that while the auditory and visual centers for words were not normally developed, and while the center for the memory of words from lip reading was just developing, it would be inevitable that he would develop idioglossia. The idioglossia in this case represents an extreme form of mispronounced and ill-expressed conventional language. They conclude that the case illustrates the interdependence of each and every elementary part of speech mechanism and especially the dependence of normal speech development upon the appreciation of variations in sounds. They believe that the speech mechanism cannot be divided into clearly defined "centers" but must be regarded as a physiologic mechanism which functions as a complete whole. As to the cause of this disorder they consider the balance of evidence to be in favor of a biological variation or of a local aplasia but state that birth injury cannot be definitely excluded.

The Relation of the Spirocheta Pallida to the Pathological Changes of Dementia Paralytica.—SMYTH (*J. Ment. Sci.*, 1928, 74, 687) attempts to correlate all the clinical and pathologic factors of dementia paralytica. Fifty-two cases of general paralysis, a few cases showing syphilitic changes in the cerebral arteries and two apparently normal brains for control purposes were examined. The patients had all been followed clinically. Spirochetes were found in 38 cases (72 per cent) of general paralysis by use of Jahnke's stain. They were not found in any of the other cases. They were found in the gyrus rectus in 32 cases; prefrontal, 34; psychomotor, 27; temporal, 26; visual, 5. Of the cases in which spirochetes were found in the visual region 2 were of the juvenile type. They were found most readily in fairly rapid subacute cases and in the childish, emotional, euphoric types and cases of the melancholia type. In very acute cases with mental confusion and rapid exhaustion and in the slow, dull, confused type with progressive dementia the spirochetes were absent or occurred in scanty numbers. Chronic cases showed a similar variation, those of the grandiose or emotional type showing spirochetes in large numbers, those of the confused, demented variety having few or none. He finds that convulsive and paralytic attacks have no relation to the number of spirochetes present. He discusses at length the lymph circulation in its relation to path of infection and believes that the subacute cases are lymphogenous in origin while the more acute cases are probably hematogenous. He believes that because of the toxicity of the cerebrospinal fluid, nervous tissue is not likely to be a favorable medium for the growth of spirochetes and he would

account for the alterations in the period of incubation of the organism in nervous tissue on this basis. The vascular changes in general paralysis, he finds to be not dependent on the local presence of the spirochete but to be part of a general pathologic change. The same contention he holds for cerebral wasting which he believes takes place in the cerebrum in reverse order to that of the evolution of its parts. He finds a distinct correlation between the presence of spider cells and neuroglia fibers in the deeper cortical layers and the presence of spirochetes. Cellular infiltration of the cortex with neuroglial cells, plasma cells and lymphocytes is also associated with the number of spirochetes present. In view of the clinicopathologic relationships advanced here he finds an interesting association with the fact that the best results of therapy by malaria inoculation and tryparsamid have been obtained in grandiose cases and in those with agitated melancholia, while in the confused and demented types little or no improvement has followed. He believes that infection of the central nervous system takes place early in the course of syphilis and advises routine examination of the cerebrospinal fluid in early cases. "A well known pathologist has recently made the surprising statement that lumbar puncture is not justifiable in cases of early syphilis since only 2 per cent show any change in the cerebrospinal fluid, yet it is a significant fact that only 2 per cent of all cases of syphilis develop general paralysis, thus it is not unlikely that cases of early syphilis which show changes in the cerebrospinal fluid are potential paretics, and it is to such cases that our present therapeutic methods might, with advantage, be applied."

Dystonies.—AUSTREGESILO and MARQUES (*Revue Neurologique*, 1928, 2, 562) present a discussion of the intermittent spasmodic dystonies. They consider that these cases represent a variety of conditions which can be divided primarily into pure dystonies and dystonic states. In the latter the symptoms of dystonia are mixed with signs of other lesions of the central nervous system such as Wilson's disease, pseudosclerosis, double athetosis, and various encephalopathies of children. From a review of the literature and their own pathologic studies they conclude that in general the lesions are in the region of the striate body. They present 5 cases in some detail. They feel that the dystonia may appear slowly and progressively at puberty with a progressive degeneration resembling Wilson's disease or perhaps may occur as the result of infectious illness often after epidemic encephalitis in which case one can usually demonstrate other concomitant syndromes. A study of the clinical and pathologic findings in these conditions has been greatly furthered by the occurrence of epidemics of encephalitis which have greatly increased the numbers of cases to be observed. Contrary to former opinions that the dystonies were encountered only in Russian or Polish Jews they have collected a number of cases in a great variety of races and their own cases occurred in both native and Spanish Brazilians.

An Apparatus for the Induction of Muscular Relaxation and Sleep.—ROSETT (*Arch. Neurol. and Psychiat.*, 1929, 22, 737) describes an apparatus, the action of which is to produce a wave of encircling pressure applied to the periphery of the body and limbs in the direction of the

venous flow. By using this apparatus he obtained muscular relaxation and, in most persons, sleep which he ascribes to a physiologic state of nerve inhibition. He finds that patients subjected to the action of the apparatus a number of times appear to contract a habit of relaxation in that they rest better at night and go about their business and pleasure in a more deliberate and systematic manner and show a general improvement in nutrition. During the action of the apparatus the blood pressure, both systolic and diastolic, is reduced in certain cases, especially in those with high blood pressure, but remains unaltered in others and in some cases shows a reduction at certain times and not at others.

PATHOLOGY AND BACTERIOLOGY

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Prenatal Volvulus of Small and Large Intestine Caused by a Mesenteric Cyst.—Owing to the various types of structure which may appear as cysts between the layers of the mesentery of the small intestine confusion has arisen in efforts to classify them. SALA and NACHAMIE (*Arch. Path.*, 1929, 8, 180) suggest the classification of purely enterogenous cysts, which they believe originate in a process of sequestration during embryonic life, into: (1) Cysts in the wall of the intestine; (2) cysts extending into the mesentery; (3) cysts extending into the lumen of the intestine. They report a case of enterogenous cyst which arose before the descent of the cecum and produced a prenatal volvulus of the small and large intestine in a full-term, female, colored child. The cyst, oval in shape, measuring 8 cm. in its longest diameter, and included between the leaves of the mesentery, was contiguous along the line of attachment of the mesentery with a loop of small intestine which was stretched and flattened over it. There was an obstruction of the jejunum above the tumor. The cyst wall was formed by mucosa, inner circular and outer longitudinal muscle layers and serous coat. The inner circular muscle layer of the cyst split to encircle the adjoining intestine at the junction of cyst and bowel and the outer longitudinal layer was common to both. In view of these histologic observations they suggest that such a cyst should be treated by resection of the involved loop of bowel.

Leukocyte Content of Regional Lymphatics in Inflammation.—MENKIN and FREUND (*Arch. Path.*, 1929, 8, 263) were able to collect and study the lymph, draining an area of inflammation produced in the fore-leg of the rabbit by the injection of sterile irritants. While it was demonstrated that the cellular content of a comparable normal lymph-

atic vessel in the rabbit consisted almost entirely of lymphocytes, polymorphonuclear leukocytes always appeared in the efferent lymphatic vessels of the regional lymph node of the inflamed area. Monocytes and clasmatoocytes were also frequently observed in the lymphatics draining the area, but their presence was less constant than that of the polymorphonuclears. The inflammatory reaction studied by microscopic sections, was observed to have involved the regional lymph node as well as the site of injection. It is pointed out that in inflammation the lymph circulation offers a path of return of some of the migrated leukocytes to the blood stream.

Undulant Fever in the United States.—There has appeared in the last few years a very extensive literature on undulant fever, indicating a greatly increased incidence, and although it is possible, it cannot be positively asserted that this is due to its recognition and separation from formerly obscure fevers. BLUMER (*Ann. Int. Med.*, 1929, 3, 122) has pointed out that the increase has not occurred among persons connected with the goat industry, and only a few infections have been related to porcine or human contact. The vast majority of cases, however, have occurred in people not in contact with goats or hogs but rather with cow's milk. Nevertheless, the evidence suggests that it is of porcine rather than of bovine origin. This means that a great deal more must be known of the epidemiology of this disease before, as the author emphasizes, any laws or regulations for its control are put into effect.

Changes in the Intestinal Flora After Partial Gastrectomy.—Many untoward effects in the general physiology of the digestion have been explained as the result of interference with the gastric secretions particularly in various grades toward achlorhydria. PORTIS (*Surg., Gynec. and Obst.*, 1929, 48, 470) finds that subtotal gastrectomy results in a change in the upper intestinal flora of dogs so that it comes to assume the fecal character of the lower intestine. These changes did not follow gastroenterostomy and as the other technical procedures were the same the negative results are useful controls to indicate the dominance of the altered gastric secretions so that there is a loss of bactericidal activity, a more rapid emptying time of the stomach and an alkaline medium in the jejunum.

HYGIENE AND PUBLIC HEALTH

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Undulant Fever.—HARDY (*J. Am. Med. Assn.*, 1929, 93, 891) presents some of the salient points in the knowledge of undulant fever.

He states that the characteristics of *Brucella melitensis* have only recently been fully described. A classification of strains isolated from human beings cannot now be regarded as a reliable index of the importance of the different varieties as a cause of human disease. A special effort should be made to obtain a detailed postmortem study in all fatal cases of undulant fever. The pathologic lesions and clinical signs of *Brucella melitensis* infections in animals show a definite correlation. The epidemiologic data, based on the reports of more than a thousand recent cases of undulant fever in the United States, indicate that cattle and hogs with contagious abortion are the source of these infections. Macroscopic agglutination tests on patients with febrile illnesses of undetermined etiology should be made more frequently. Additional study is essential in order to determine effective and applicable methods of control. KING (*New England J. Med.*, 1929, 201, 918), who has made a study of *Brucella abortus* infection of milk, states that contagious abortion is widely prevalent in cattle throughout the United States, and that approximately 20 per cent of raw market milk is infected with *Brucella abortus*. Both bovine and porcine strains are pathogenic for man. It is impossible to specify any given serum agglutinin titer as diagnostic of undulant fever. Ingestion of infected milk and direct contact with infected animals are the chief causes of undulant fever. Either universal pasteurization of milk or a new code of certification of milk is essential in the control of undulant fever. That undulant fever is a public health problem is indicated by the increasing number of cases being reported.

Cancer Studies in Massachusetts. III. Cancer Mortality in Nativity Groups.—LOMBARD and DOERING (*J. Prev. Med.*, 1929, 3, 343) state that a sufficiently close correlation exists between the social classes in England and the nativity groups in Massachusetts in respect to the cancer death rate to warrant the opinion that economic social conditions are a factor in the causation of cancer. The foreign born have much higher rates than the native born of native parents in cancers of the buccal cavity and the stomach. Cancer of the stomach is abnormally high among both males and females for all foreign-born groups, and cancer of the buccal cavity among the Irish, English and Teutons. Cancer of the lower intestinal tract in females is high among the Irish and English, while it is low among the Italians. The Canadians have a high rate for cancer of the uterus, and the Russians a low rate. Both the Italians and the Russians have low rates for cancer of the breast. The Irish and the Italians show higher rates in Boston than in their native countries. The sex ratio (females per male) is much higher for the native born of native parents than for any of the foreign nativity groups which have been studied in Boston and Europe. The Irish have slightly poorer diagnostic facilities than the other foreign groups, but the foreign born taken as a whole have sufficiently good diagnosis to eliminate the factor of diagnosis in discussing the high cancer death rate of the foreign born.

Leprosy in the United States.—A statistical study of 700 cases in the National Leprosarium: Hopkins and Denney (*United States Pub. Health Rep.*, 1929, 44, 695) summarize their study as follows: A statistical study of 718 lepers hospitalized over a period of 34 years in the Louisiana Leper Home, later the National Leprosarium, was made. Two hundred and fifteen were foreign born, and 503 were natives of the United States. The present population of the hospital is 287. Mexico, China, Italy, Greece, and the Philippine Islands have furnished one-half of the total foreign born. Most of the lepers came from Louisiana, California, New York, Texas and Florida; 418 came from Louisiana. The incidence of leprosy among the white population of Louisiana is computed to be twice that in the negro. Of the total cases, 11 per cent were of the nerve type, 39.1 per cent of the skin type, and 49.9 per cent of the mixed type. Of the total cases, 72.3 per cent were in males and 27.7 per cent were in females. The social status of the patients represents a cross section of the normal populace. The average age at onset of the disease is computed as 30.2 years; the average age on admission to the hospital was thirty-six years, with an average period of six years prior to admission, during which time each patient may have been a menace to public health. In a group of 100 Louisiana lepers, hospitalized more than fifteen years ago, it has been disclosed from subsequent records that in 64 instances only one leper in the family developed the disease, while in the 36 other instances leprosy occurred in 83 additional relatives. In some families the disease has invaded certain branches to the point of extermination. Instances of familial transmission have also been noted in cases from other States than Louisiana. It has not invariably happened that the parent became infected before child; indeed, the reverse frequently occurred. Intimate contact over a period of time extending into years has been concurrent in most instances of familial transmission; in many cases multiple contacts also existed. In 5 cases the incubation period is calculated as not less than six years. The first manifestation of leprosy was recalled by most patients as one or more spots appearing on the face; in no instance were conditions described that might be identified as prodromal symptoms or as the initial lesion of leprosy. Aside from the increased number of cases developing in males at about twenty-one and in females at about nineteen years, and the counterbalancing rarity of leprosy before the age of nine years, the disease appears to manifest itself at all ages about equally. The duration of leprosy is computed as approximately fourteen years. It appears that leprosy greatly shortens the life expectancy of the young, but has less effect on the life expectancy of the aged. The mortality rate has gradually decreased in the hospital since its organization. Leprosy *per se* has been the cause of death in less than 20 per cent of the lepers; respiratory, renal, and cardiac disorders indirectly dependent on leprosy have caused more than one-half the deaths. Before rigid rules for paroles were promulgated, relapses of discharged cases were not uncommon; but in the last seven and a half years 28 lepers have been paroled and only 1 has relapsed and been readmitted.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 16, 1929.

Energy Expended in Maintaining a Muscular Contraction.—D. W. BRONK (Eldridge R. Johnson Foundation, University of Pennsylvania). The recent work of ADRIAN and BRONK (*J. Physiol.*, 1928, 66, 81; 1929, 67, 119) has shown that the grading of a reflex or voluntary muscular contraction depends largely on a change in frequency of the motor nerve impulses. This frequency was found to vary from as low as 5 or 10 to 100 a second, which would indicate that a weak contraction is maintained by asynchronous series of twitches in the several muscle fiber groups, while a strong response is produced by a fused tetanus of the active fibers. In order, therefore, to determine the economy of energy expenditure in maintaining contractions of varying strengths the heat production and tension time have been measured at various frequencies of stimulation. As the rate of stimulation is increased, the economy or amount of tension-time maintained per unit of energy expended increases. This is primarily due to a greater degree of fusion of the separate muscle twitches, there being no increase in economy with frequencies of a value higher than that needed to produce complete tetanus. It may be concluded, therefore, that tension is maintained with a smaller expenditure of energy in a strong contraction than in a weak one.

It is a well-known fact that a stimulation frequency not quite sufficient to give partial summation of the successive twitches will, if continued, produce a fused tetanus. This altered character of the response is due to progressive fatigue. In order, therefore, to determine the economy of maintaining tension throughout the development of fatigue, a muscle has been stimulated in nitrogen at a frequency of about five a second for a period of three minutes and the rate of heat production and tension time developed has been measured. The results of these experiments show that a unit of tension is maintained with a lower expenditure of energy as the muscle fatigues. This fact is of probable importance in connection with long-sustained contractions.

The Influence of Electrolytes on Certain Types of Hemolysis.—M. H. JACOBS (Department of Physiology, University of Pennsylvania.) Although the mammalian erythrocyte is structurally a very simple type of cell whose properties might be expected to remain fairly constant under a variety of external conditions, it is, in reality, extremely sensitive to slight changes in its environment. Certain striking effects of low concentrations of salts upon hemolytic processes are here reported.

In the case of simple osmotic hemolysis where the entrance of water into the erythrocyte is the factor chiefly involved, low concentrations of nonelectrolytes of the order of 0.01 or 0.02 M have a barely detectable effect. Hemolysis in such solutions is almost as rapid as in distilled water. To double the time required to reach a certain degree of hemolysis in solutions of nonelectrolytes concentrations of the order of magnitude of 0.10 M are necessary. In the case of electrolytes, on the other

hand, a noticeable retarding effect was found with the following concentrations: NaCl, 0.001 M; CaCl₂, 0.0001 M; Al₂Cl₆, 0.00004 M, while the time for hemolysis was doubled in 0.005 M, 0.0012 M and 0.0002 M solutions, respectively.

The effect of salts on the rate of osmotic hemolysis involving the penetration of a dissolved substance as well as water may sometimes be of a different nature. Thus, the time required for human erythrocytes to reach 75 per cent hemolysis in 1 M glycerol was in a typical experiment diminished by 0.01 M NaCl from 245 to 110 seconds and that for ox erythrocytes to reach 83 per cent hemolysis in 0.125 M glycerol was similarly diminished by 0.0025 M NaCl from 332 to 11 seconds. In experiments of this type involving hypotonic solutions an apparent retarding effect on the penetration of water and an apparent accelerating one on the penetration of glycerol may coexist and give to the entire process a considerable complexity. The accelerating effect of salts on hemolysis by penetrating substances seems to be limited to compounds like glycerol which penetrate with difficulty.

Neutral salts also have a very pronounced accelerating effect on hemolysis by certain concentrations of acids. The time of penetration of 0.012 N HCl from isotonic nonelectrolyte solutions into erythrocytes, as judged by the color change produced by the formation of acid hematin within the cells, is considerably accelerated by small amounts of NaCl and CaCl₂. The effect of Na₂SO₄ on penetration is similar to that of NaCl and CaCl₂ but certain concentrations of this salt greatly retard hemolysis or prevent it altogether.

The Contractility of the Gall Bladder.—I. S. RAVDIN, (Department of Research Surgery, University of Pennsylvania). Several methods have been used in order to determine whether or not the gall bladder is capable of emptying its contents through the cystic duct. If the bile which once enters the cystic duct does not leave the gall bladder by the same route, bile pigment should be present either in the cystic lymph vessels or an increase in bile pigment should be obtained in the cystic vein blood. The cystic lymph fluid of the dog or cat does not contain bile pigment nor does the cystic vein blood contain a larger amount of this than is present in the peripheral venous circulation. That the gall bladder can empty materials (carbon particles or dyes) through the cystic duct can be demonstrated by placing these materials in the gall bladder after ligating all ducts, other than the cystic duct, which enter the common duct and then stimulating gall bladder contraction either by a fat meal or by drugs. The substances can then be found in the duodenum. The isolated gall bladder of the dog, guinea pig, and rhesus monkey have been studied in a constant temperature bath (38.5° C.). They all show rhythmic contraction and respond to certain drugs as one would expect. Histamin, pilocarpin, physostigmin and barium chlorid cause an increase in tonus while adrenalin and atropin cause a relaxation of the muscular activity.

Intraperitoneal and Intrapleural Pressure Relationships.—RICHARD H. OVERHOLT (Department of Research Surgery, University of Pennsylvania). A method was devised for the insertion of a cannula through the anterior abdominal wall into an intraperitoneal space and through the chest wall into the intrapleural cleft so that the variations in intra-

pleural pressure coincident with abdominal manipulations could be studied. Anesthetized and unanesthetized dogs were used. A water manometer and a membrane manometer which was later calibrated were used to register pressures. It is impossible to register the true intraperitoneal pressure by the method used, but the method served as a basis of comparison with similar types of procedures which have been carried out by other investigators. On introducing the cannula into the abdomen, the pressure at the point of measurement was always found to be subatmospheric. With the dog in the head-up position, the subatmospheric pressure increased with the cannula in the epigastrium. In the head-down position and the cannula in the same position, the subatmospheric pressure approached atmospheric pressure or became slightly positive. By the method used it was impossible to record marked variations in intraperitoneal pressure after manipulation of the abdominal wall or distention of the stomach or colon unless pneumoperitoneum was present. However, abdominal manipulations with or without the presence of pneumoperitoneum affected the intrapleural pressure. After pneumoperitoneum, the intraperitoneal pressure was increased greatly by the application of an abdominal binder, inflation of the stomach, or a shift in position. The presence of small amounts of air in the peritoneal cavity had little or no effect on respiratory movements or on the intrapleural pressure. If 50 cc. or more air per kilogram were injected intraperitoneally, the amplitude of the intrapleural tracing was increased and the intrapleural pressure at the end of expiration approached atmospheric pressure. The rate of respiration was increased. Incision of the abdominal wall caused a decrease in rate and an irregularity of the excursions. The intrapleural pressure at the end of the expiratory phase approached atmospheric pressure or became slightly positive. The application of pressure or a binder to the abdomen affected the intrapleural pressure to a greater extent when air was present within the peritoneal cavity. The same holds true for the effect of inflation of an intragastric balloon. Phrenic nerve stimulation increased the subatmospheric pressure in the pleural space on the same side. Vagal stimulation stopped respiration with equal pressures in the two pleural cavities.

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ORIGINAL ARTICLES.

THE NEPHROPATHIC EFFECT IN MAN OF A DIET HIGH IN
BEEF MUSCLE AND LIVER.*

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IN a recent publication¹ we showed that rats that lived on diets high in animal tissues (muscle and liver) gradually developed chronic sclerosing kidney disease. While it is generally believed that such results have a bearing on disease in man, any conclusions regarding him formed on the basis of such indirect evidence, are open to doubt. It is accordingly highly desirable to record the response to diets of this type in man himself.

We have had the opportunity of obtaining this information. The subject, a member of the laboratory staff, was an apparently normal man, aged thirty-two years.

During a preliminary period of thirty-five days he took a diet containing less than 100 gm. of protein daily, of which roughly 50 gm. were of animal origin.

During this time several careful physical examinations revealed no abnormalities. The blood pressure in the basal state was

* The expenses of this investigation were defrayed in part by a fund for the study of nutrition created by Mr. W. K. Kellogg of the Kellogg Corn Flake Company, Battle Creek, Michigan.

110 mm. systolic and 80 mm. diastolic. The nonprotein nitrogen of the blood was 31 mg. per cent. Three untimed fresh specimens of urine were tested for albumin by boiling and acidulating, with negative results; and for casts, of which a few were seen in one sample but none were noted in the two other specimens.

Addis² has shown that a few casts are usually present in the urine of normal persons and has emphasized the desirability of recording the number of casts voided in a unit of time as a criterion of the state of the kidneys. Three specimens were examined according to Addis' method. The subject saved all the urine from bedtime until 8 o'clock the next morning. None of the specimens contained enough albumin to be detectable by the usual clinical methods. The cast counts were respectively 49, 48 and 52 per hour. The urines were acid. Addis made 82 examinations of the night urines collected for twelve hours by 74 medical students. No casts were seen in 29 instances. The highest count gave 356 casts per hour and the average for the whole series was 87 casts per hour.

During the next six months, from April 10 to October 21, 1928, our subject received a diet specially prepared for him under the direction of Miss M. M. Harrington. Its composition according to the figures found in the standard food tables was as follows:

Protein	338 gm.
Fat	271 gm.
Carbohydrate	96 gm.

The calory value was 4177. Of the protein, 327 gm. were of animal origin and were contained in the following foods:

	Amount eaten.	Protein.
Fresh beef liver	about 400 gm.	80 gm.
Fresh veal round	about 300 gm.	60 gm.
Fresh beef tenderloin	about 700 gm.	164 gm.
Dried beef	about 100 gm.	33 gm.
		<hr/>
		337 gm.

About one-quarter of the protein was contained in the liver.

In addition to these meats, the diet contained an adequate supply of vitamins and inorganic constituents in the form of butter, green vegetables and citrus fruits. Only 31 per cent of the calories of the diet were contained in the animal protein.

This diet caused no subjective disturbances. The retinae remained normal. Of special interest is the fact that the blood pressure was unaffected by the diet.

The urine was examined twenty-five times during these six months. Albumin made its appearance for the first time after the subject had been on the diet for six weeks. Henceforth there was a gradual increase in the cloud caused by boiling and acidulating the filtered urine. However, the albuminuria was not great enough

to permit its measurement by the sulphosalicylic acid method³ until the sixth month, when the subject was excreting 2 to 4 mg. of protein per hour.

The cast counts are contained in Table I. It will be seen that the counts during the first seven weeks (April 17 to June 5) were within the normal range based on Addis' experience. After that, the counts were definitely in the pathologic field. During the former period the highest count was 413 and the average of the seven counts was 216. Whereas during the final six weeks, the highest count was 3540 and the average of the ten counts was 1283, which is fifteen times the average obtained by Addis in controls.

TABLE I.—INCREASE IN CYLINDRURIA FROM HIGH MEAT DIET.

Date.	Casts per hour.	Date.	Casts per hour.
April 17	177	July 11	1109
April 19	84	July 11	1735
May 9	232	July 19	1856
May 17	104	September 9	400
May 23	413	September 12	1895
May 29	360	October 1,	0
June 5	142	October 8	952
June 12	1053	October 10	2048
June 19	1083	October 11	3540
June 26	601	October 17	0
June 29	1680	October 20	1500
July 10	974	October 22	2500

In addition, a change in the appearance of the casts took place as time went on. In the early weeks they were hyalin. Gradually more and more granular casts were seen. During the last weeks some of the casts were cellular and the hyalin variety was in the minority.

The urines were always acid, with a pH that was close to 5. The specific gravity varied from 1022 to 1027.

In order to make certain that the counts were not influenced by the desire of the observer, the following procedure was carried out during the last month. An associate prepared the urine from the subject and from himself and other controls, in the absence of the observer. The latter then made counts of specimens whose identity were unknown to him. In the urines of the controls he found 0, 20, 30, 197 and 213* casts per hour.

The high meat diet was discontinued on October 22. Thereafter the subject followed his own choice. He avoided meat and preferred carbohydrate. The urine examinations made after the change in diet are recorded in Table II. Recovery was complete in ten days.

The evidence reported makes it clear that a diet of which 31 per cent of the energy was contained in beef proteins caused a slowly

* From an individual who was suffering from acute rhinitis at the time.

increasing albuminuria and cylindruria* in our human subject. The continued excretion of these urinary abnormalities in noteworthy amounts indicates that the kidneys were being harmed by the diet.

TABLE II.—RECOVERY FROM HIGH MEAT DIET.

Date.	Albumin.	Casts.	Reaction.
October 24	Trace	1778	Acid
October 26	V.S.T.	980	Acid
October 27	S.P.T.	690	Acid
October 28	S.T.	140	Acid
November 2	0	0	Acid

When comparison is made between man and the white rat it must be remembered that the life span of the former is twenty times that of the latter and, therefore, six months in the life of a man corresponds to less than two weeks in that of the rat.

We have fed a group of 7 rats a diet 33 per cent of whose calories were contained in the proteins of beef muscle. The urines were examined for the first time when the animals had been taking this diet for more than one month. There was no increase over the usual trivial albuminuria found in normal rats. No casts were seen in 6 of the specimens. The seventh contained a few. Our experience with a similar type of diet, except that beef liver replaced the beef muscle, was the same.

A diet capable of producing a pathologic urine in a man was without detectable effect on the urine of the white rat. The kidneys of a man appear to be more easily injured than are those of the white rat by diets high in animal tissues.

TABLE III.—TOTAL URINE NITROGEN AND SOME OF ITS FRACTIONS FOR TWENTY-FOUR-HOUR PERIODS WHILE SUBJECT WAS EATING HIGH MEAT DIET.

Date.	Total N.	Uric acid.	Amino-acid N.	Creatinin.
July 24	57.0	1.16	0.48	2.54
July 25	57.5	1.84	0.43	2.37
July 26	60.5	1.91	0.46	2.80
August 13	54.2	1.77	0.43	2.98
August 14	51.5	2.46	0.37	2.72
August 15	55.0	1.99	0.44	2.70
October 15	45.3	1.54	0.44	2.19
October 18	54.9	1.97	0.57	2.50

Total N determined by Kjeldahl method.

Uric acid by Morris and McLeod method.

Amino acid N and creatinin by Folin methods.

There are in the literature a number of papers purporting to prove that an exclusive meat diet is not harmful to the kidneys of man. These reports, as a rule, deal with the life of the Eskimos

* In this connection, it is interesting to note that a chronic nephritic under our care at this time, with hypertension, nitrogen retention, retinitis and inability to raise the specific gravity of the urine above 1012, had an hourly excretion rate of only 5 mg. albumin and 5000 casts.

and are stated in such general terms that they are of questionable scientific value.

Recently, however, Thomas⁴ succeeded in gathering some concrete information regarding 142 middle-aged Greenland Eskimos who had always lived on a carnivorous diet. He found albuminuria in 12 persons (8.5 per cent), excluding those that had pyuria; 9 (6 per cent) had hypertension. From these figures, he draws the surprising conclusion that "There is no unusual prevalence of vascular or renal disease" among these people. The examination of 16,662 men, policyholders of the Metropolitan Life Insurance Company,⁵ revealed definite albuminuria in only 2.5 per cent of the group. The rate for men between the ages of forty-five to fifty-four years was 2.5 per cent; only 0.9 per cent showed a marked amount of albumin.

TABLE IV.—NITROGEN VALUES IN THE BLOOD DURING HIGH MEAT PERIOD.

Date.	N.P.N., mg. per cent.	Urea N., mg. per cent.	Uric acid, mg. per cent.	Amino-acid N., mg. per cent.
July 25	55.8	34.4	3.23	6.7
August 14	49.3	31.8	3.10	6.55
October 17	42.9	24.6	2.06	6.29
October 22	49.2	32.4	2.87	6.66

TWENTY-FOUR HOURS AFTER RETURN TO NORMAL DIET.

October 23	35.4	16.8	2.45	6.8
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All determinations except uric acid by Folin methods: uric acid by Morris and McLeod method.

The blood samples were taken before breakfast in the morning. The subject had a meat sandwich at bedtime.

Furthermore, it should be pointed out that the response of the Eskimos to their diet does not necessarily furnish a measure of the effect of a similar diet upon men living in the temperate zone. The present Eskimos are presumably the product of adaptation, working through many generations, to the only possible food supply. The history of the white race has been different.

Recently, Lieb⁶ has reported the failure to obtain evidence of renal impairment in the case of two arctic explorers who lived for twelve months on an "exclusive meat diet." The average composition of this diet was, in fact, such that 80 per cent of its energy was in the form of fat. Only 100 to 140 gm. of protein were eaten daily. To enhance the fat content of the meat, these subjects partook freely of suet and bone marrow. The persistent ketonuria⁷ emphasizes that the chief characteristic of this diet was its abnormally high content in fat. It is important to draw a distinction between the connotation of the word "meat" as ordinarily understood, and that given it by these writers. Since the protein content of this diet is not far different from that habitually eaten by large classes of our population, one would scarcely expect to find marked evidence of kidney disease in the period of one year. Those who suspect that

the discovery of chronic nephritis in middle life is evidence that such a diet is harmful, believe that a great many years have been required to produce a recognizable injury. On the other hand, had these observers attempted to count the urinary casts, some evidence of abnormality might have been found.

In contrast to the negative character of the observations of Lieb and Tolstoi is the fact that our subject voided an abnormal urine within a few months after he had begun to live on a diet about half of which consisted of meat in the ordinary sense of the word.

Summary and Conclusions. A human subject, whose urine contained no albumin and less than the average number of casts found in normal men by Addis, lived for six months on a diet in which one-third of the calories were contained in beef proteins. As a result, he developed a significant albuminuria and a twenty-fold increase in casts.

Our earlier work has shown that it takes a longer time, relatively, to produce abnormal urine in the white rat by similar diets. Hence results obtained by means of the rat in this field are directly transferable to man.

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THE TREATMENT OF NONTROPICAL SPRUE WITH LIVER EXTRACT.

A REPORT OF TWO CASES.

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In a recent study¹ of 45 patients having a macrocytic type of anemia 2 patients were found to present clinical phenomena and laboratory data of such distinctive character that they were grouped as a specific disease entity. Their response to treatment

with liver feeding further emphasized their differential classification and it is noteworthy that the patients were replicas each of the other in their clinical state and course.

The cardinal characteristics of the disease have been an extreme degree of emaciation, severe anemia of the macrocytic type, chronic diarrhea, normal amounts of HCl in the gastric content, a complete absence of neurological phenomena, and rapid and consistent improvement following the feeding of adequate amounts of a potent liver extract.

We identify the condition as nontropical sprue in recognition of the fact that all of the symptoms and findings noted in our cases have been observed in sprue by other students of this disease.

In the treatment of the two cases here presented we have used a general hospital diet with the addition of liver extract E29* in amounts equivalent to 630 gm. of raw liver per diem.

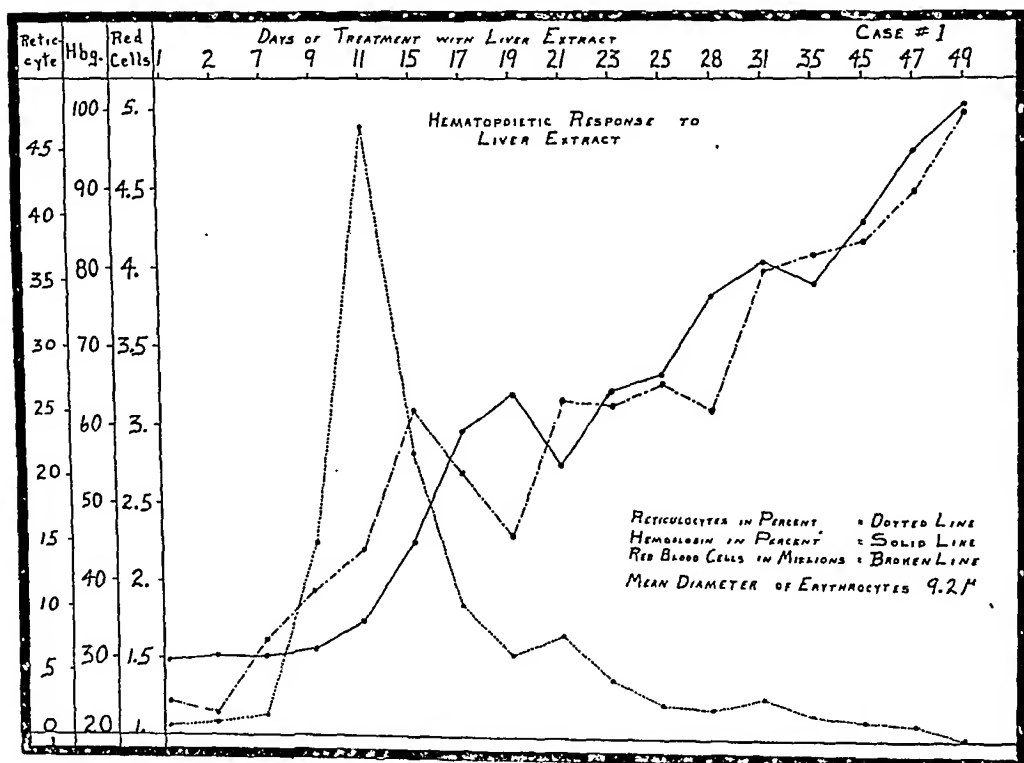


CHART I.

Case Reports. CASE I.—T. J., aged fifty-six years, an American negro, laborer, entered the hospital on August 20, 1928, complaining of recurring attacks of diarrhea accompanied with abdominal pain and rapid loss of weight, especially marked for the preceding seven weeks.

The past history is not suggestive, the patient having lived always in Virginia and until the beginning of the present trouble being always healthy and robust.

* Liver extract E29 is an aqueous extract of liver developed by the Department of Medicine and Biochemistry of the Medical College of Virginia in collaboration with the Valentine Meat Juice Company, Richmond, Va., U. S. A.

The gastrointestinal symptoms began insidiously during the month of July, 1923. Since that time they have persisted with exacerbations consisting of diarrhea (8 to 10 stools per diem) anorexia, and rapid loss of weight. During remissions, 2 to 4 stools at night and 1 to 2 during the day represented the average degree of diarrhea. The stools were liquid and light in color. At the time the patient entered the hospital the number of stools was from 4 to 6 at night and from 2 to 3 during the day, watery in consistency but frothy and light in color. There was absolute anorexia.

Physical examination showed a markedly emaciated and undernourished male, manifestly quite ill. Height 5 feet 11 inches, weight 124 pounds. The tongue was pale with no atrophy of the papilla, but the tip and margins were raw and red. The abdomen was distended, tympanitic, and gave a doughy sensation when palpated. Proctoscopic examination was negative. No abnormal neurologic changes were elicited. Roentgenographic study of the gastrointestinal tract showed a moderate degree of megacolon. The blood count was: red blood cells, 1.1 million per c.mm.; hemoglobin, 29 per cent (Sahli); leukocytes, 4200 per c.mm.; polymorphonuclears, 52 per cent; lymphocytes, 48 per cent; reticulocytes, 0.2 per cent. Mean diameter of the erythrocytes was 9.5 microns. Wassermann reaction was negative. Stools were negative for *Monilia psilosis*, amœba, ova, parasites, pus and blood, but contained an excess of fat when stained with Sudan III. Stomach analysis after Ewald test meal showed free hydrochloric acid, 15 degrees, total acidity, 34 degrees.

Treatment and Course in the Hospital. The patient could take only liquid food for the first three days, but to this was added liver extract in amounts equivalent to 630 gm. of raw liver. Chart I shows the hematopoietic response. The clinical improvement was most striking. The patient's appetite was ravenous by the end of the first week and all distressing gastrointestinal symptoms had disappeared by the end of the second week, at which time there were one or two normal stools a day. The patient was discharged from the hospital at the end of thirty-four days, apparently normal, and weighing 156 pounds, which was a gain in weight of 32 pounds. The patient was continued on the equivalent of 400 gm. of liver until January, 1929, at which time the red-cell count was 5.9 million per c.mm.; hemoglobin, 110 per cent (Sahli), and weighed 178 pounds, making a total gain of 54 pounds in four and a half months' time.

CASE II.—Mr. C. C., aged sixty-three years, white, an American tradesman, entered the hospital on February 19, 1929, complaining of diarrhea, recurring sore mouth and tongue, and progressive loss of weight, marked weakness and complete anorexia.

The past history is not suggestive, the patient having lived in Richmond, Virginia, all of his life and until the beginning of the present trouble having been physically robust.

The present illness began insidiously thirteen years previously and had continued with partial remissions since the onset. Chronic "indigestion" characterized by intestinal flatulence was a prominent symptom and he attributed the diarrhea to the gas which was marked at times. The type of stools had not been consistent in character. During the acute exacerbations there were 10 to 12 stools each twenty-four hours, 7 or 8 during the night and 3 or 4 during the day, watery in consistency, containing no blood or mucous, but gassy and irritating to the anus. In the remission, 2 to 3 stools in the early morning represented the average degree of diarrhea. These were large, soft, light in color and foamy. He had for two years attempted no work, had for a year lost much weight, and had been bedridden for two months previous to entering the hospital.

Physical examination revealed a markedly emaciated and undernourished

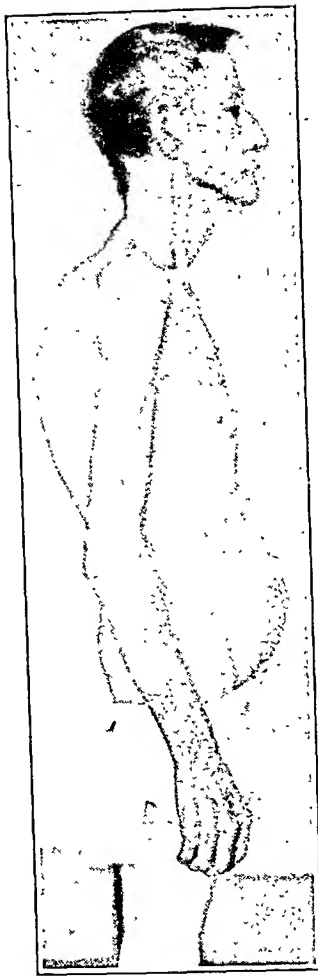


FIG. 1.—Appearance of Patient 2. Marked emaciation and lower abdominal distention. Weight 91 pounds.



FIG. 2.—Megacolon in Case 2. Two thousand cubic centimeters of barium sulphate solution used as an enema.

man, manifestly in the terminal stages of a severe illness. Height 5 feet 9 inches, weight 91 pounds. All teeth had been extracted three years previously and no artificial denture was used because of the recurring stomatitis. The tongue was pale with no atrophy of the papilla, but the tip and margins were raw and sensitive. The heart and lungs were essentially negative, but the peripheral arteries showed marked atheromatous changes of the Mönckeberg type, with a blood pressure of systolic 100 and diastolic 55. The abdomen was distended and tympanitic, but with no localized tenderness, and the size of the liver and spleen was apparently normal. There was edema of the feet and ankles extending to the middle of the leg. The neurologic examination was negative throughout. Proctoscopic examination was negative, and the roentgenographic study of the gastrointestinal tract was negative, except for a marked degree of visceropptosis and a moderate degree of megacolon (Figs. 1 and 2).

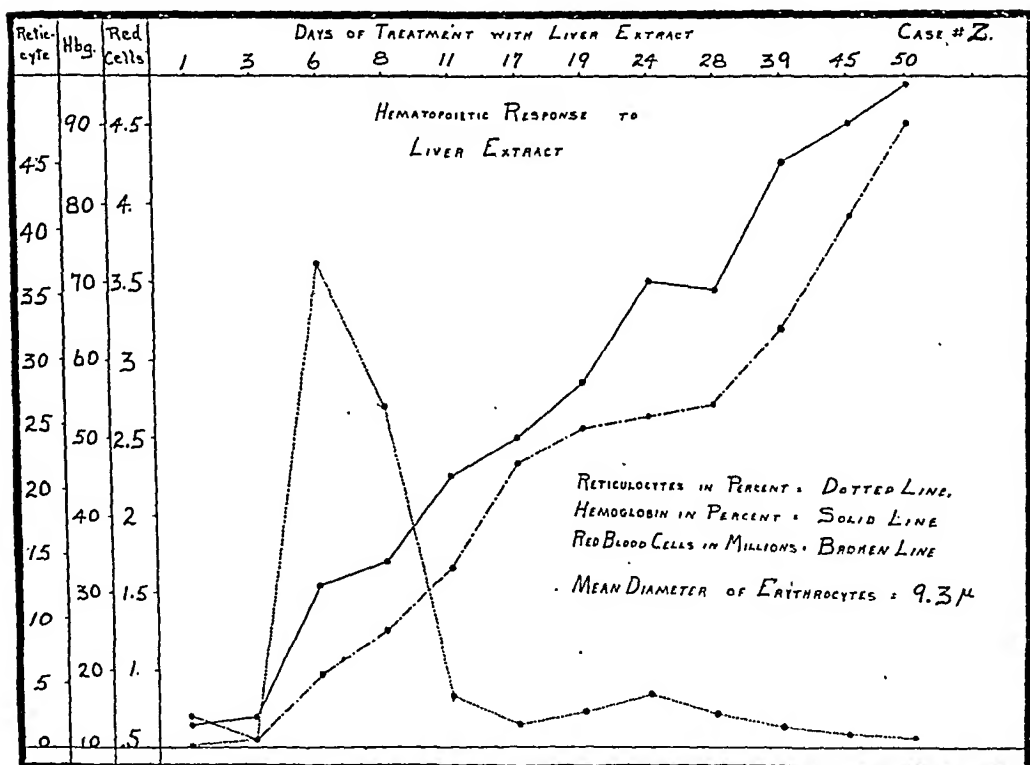


CHART II.

Laboratory Data. Hemoglobin, 13 per cent (Sahli); red blood cells 640,000 per c.mm.; white blood cells, 3800 per c.mm.; polymorphonuclear neutrophils, 12 per cent; eosinophils, 1 per cent; lymphocytes, 87 per cent; occasional normoblast; marked anisocytosis; poikilocytosis and slight polychromatophilia; reticulocytes, 0 per cent. Mean diameter of the erythrocytes was 9.3 microns. Wassermann reaction, negative. Stomach analysis after Ewald test meal showed free hydrochloric acid, 48 degrees, total acidity, 69 degrees. Stools were negative for blood, ova, parasites, *Monilia psilosis* and excess of fat with Sudan III. Blood calcium, 8.9 mg. per 100 cc.

Treatment and Course in the Hospital. The patient could take only liquid nourishment which was supplemented with liver extract in amounts equivalent to 630 gm. of raw liver. Chart II shows the hematopoietic response. The clinical improvement was most striking. Within five days

the patient's appetite was ravenous and he was taking a general diet. All distressing gastrointestinal symptoms, together with his stomatitis had disappeared by the twelfth day, and there were one or two normal stools a day. The patient was discharged from the hospital at the end of forty-nine days, weighing $127\frac{1}{2}$ pounds—a gain of $36\frac{1}{2}$ pounds, and apparently well. He was last seen on May 14, 1929, at which time his weight was 136 pounds. He stated that he felt well and was able to work as a shoemaker, eight hours a day.

Discussion. The diagnosis of sprue is still on an unsatisfactory basis. During the early stages of the disease it may be confused with a large group of heterogeneous intestinal disturbances; some of which may eventually develop a clinical picture characteristic of the genuine disease. In the late stages of sprue much diagnostic confusion may rise, because of the existence of symptoms and phenomena common to other disease entities, notably pernicious anemia.

The cases here presented did not show the Ashford monilia, nor the characteristically "fatty" stools at the time of admission to the hospital. It may be noted, however, that no quantitative estimation of fat was made. The diagnosis of nontropical sprue instead of pernicious anemia was favored because of the finding of adequate quantities of hydrochloric acid in the stomach content, the absence of physical findings indicating spinal cord lesions, and the marked degree of emaciation. The response to liver feeding was even more striking than that observed in Addisonian anemia, and similar results in sprue have been reported by Bloomfield and Wychoff,² Minot and Murphy,^{3,4,5} Ashford⁶ and Williams.⁷ Holmes and Starr⁸ have recently reported a series of 5 patients presenting a clinical picture characterized by emaciation, anemia, tetany, chronic diarrhea, low blood calcium and malabsorption of fat. Therapeutically they used a diet consisting of a low carbohydrate and fat content. The hypodermic administration of parathyroid extract was prescribed to control the disturbed calcium metabolism, but no liver feeding was attempted. The cases presented by these observers are strikingly similar to the patients reported in this series and probably represent the same clinical entity.

The nature of the anemia occurring in sprue has for many years been a topic for much discussion. Smith,⁹ and Baumgartner and Smith¹⁰ have expressed themselves as believing that the anemia of sprue is aplastic. Reed and Ash¹¹ in discussing "atypical sprue" mention a group of 11 cases observed in the Philippines with advanced anemias "invariably aplastic in type and progressive in spite of all treatment." Ashford,⁶ commenting on the results in 14 patients with tropical sprue treated with liver extract noted that the 10 patients having an anemia of the "primary type" all improved, but the 4 patients having a "secondary type" of anemia showed not the slightest response to liver extract. The hemato-poietic response in our patients having nontropical sprue and in the

cases of sprue reported by other American observers using whole liver or liver extracts would indicate that the anemia is neither aplastic nor secondary, but dependent upon a disturbance of bone marrow physiology similar to that found in Addisonian anemia.

The finding of adequate amounts of hydrochloric acid in the stomach contents of patients who have blood pictures of an advanced macrocytic anemia, but without phenomena indicating a myelitic process, strongly suggests that the megaloblastic anemias may be dependent upon an independent factor, and the absence of neurologic pathology in the cases here reported would indicate that the presence of normal gastric enzymes had functioned as a prophylactic agent, protecting the organism against the development of neurotoxins; a complication so consistently found in pernicious anemia. One cannot escape the conviction that this is a useful working hypothesis and that adequate amounts of hydrochloric acid should be administered routinely in the treatment of patients having a primary type of anemia and achylia gastrica regardless of how completely the blood has been restored to normalcy with liver feeding.

Summary. 1. Two patients presenting clinical characteristics of sprue with marked degrees of macrocytic anemia but without monilia psilosis in the stools or on the mucous membranes of the mouth, have been treated with liver extract with prompt relief of all symptoms of the disease.

2. The hematopoietic response to liver indicates that the anemia was neither secondary nor aplastic, but associated with a megaloblastic hyperplasia of the bone marrow and was fundamentally of the same type as the anemia of Addison.

3. The prompt relief of intestinal disturbance by the use of that substance contained in mammalian liver is most striking and suggests that the anemia and its associated disturbance of intestinal physiology may be essentially a deficiency disease; and that nontropical sprue is not a moniliasis of the digestive tract.

4. The notable absence of all neurologic phenomena in patients having advanced degrees of macrocytic anemia with normal amounts of hydrochloric acid in the gastric content suggests that the spinal cord changes in pernicious anemia are definitely related to the achylia gastrica found in that disease.

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THE RELATION OF CHOLESTEROL, LECITHIN PHOSPHORUS AND FATTY ACIDS TO THE REMISSION OF PERNICIOUS ANEMIA.

WITH THE TECHNICAL ASSISTANCE OF EMILIE GOODE AND MIRIAM
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IN the opinion of many investigators, disordered cholesterol metabolism is an important aspect of the disease pernicious anemia and of the so-called hemolytic anemias. This opinion has been fostered mainly by two facts, namely: that cholesterol is an anti-hemolytic agent¹⁻⁶ and that usually cholesterol is reduced in anemias of this type and consequently this lack may play a rôle in the causation of these anemias.⁷ This conviction of the importance of cholesterol in pernicious anemia is reflected in the literature where a number of reports are found describing its therapeutic use, with results varying from ineffectiveness to considerable improvement.⁸⁻¹⁵ MacAdam and Shiskin¹⁶ point out that when the patients improve there is conclusive evidence of increased cholesterol in the plasma and decreased hemolytic activity. This has subsequently been confirmed by others.¹⁷⁻¹⁹ The opinion of Bloor²⁰ that the low values for cholesterol in the plasma of pernicious anemia patients are not without significance in view of the part cholesterol is said to play in protecting corpuscles from the action of hemolytic agents, has been voiced by many investigators^{17, 21-25} while others²⁶⁻²⁸ have advanced the opinion that the general disturbance of the lipoid metabolism of the body is the primary cause of the disease. McNee²⁹ however, refuted the idea that the low cholesterol in pernicious

anemia patients is due to the utilization of this substance as an anti-hemolytic agent.

A relation between red blood cell destruction and the amounts of lipoids in the blood was suggested by Erben in 1902.³⁰ From studies concerning the lipoid metabolism in chlorosis he concluded that blood destruction does not take place in this disease because the lipoids in the blood were not increased, and, in fact, he found them decreased. He thought that if there was a great destruction of red blood cells, the lipoids would be increased, and this would be so much more marked in chlorosis as the fat metabolism is impaired.

Experimentally it has been shown that destruction of erythrocytes *in vivo* caused an increase of cholesterol both in the blood, bile and feces.³¹⁻³⁴ Bodansky,³⁵ however, obtained a variable result in dogs. In contrast to the experimental work stand the human anemias of the so-called hemolytic type, many of which show a decrease of cholesterol and lecithin in the blood. The picture is still further confused by the fact that low cholesterol values are found in other types of anemia in which increased blood destruction cannot be demonstrated.

This has led some observers to conclude that the number of red blood cells, that is, the anemia, is directly related to the level of the cholesterol. This opinion has been voiced by Schnabel³⁶ and Strathmann-Herweg,³⁷ who concluded that the anemia itself, not a hypothetical toxin causing the anemia, must be responsible for the low cholesterol in the blood. Bloor³⁸ suggested that inasmuch as there is considerable evidence to show that the red blood cells participate in the fat metabolism, the low values of lecithin may be regarded as due to deficient fat assimilation from the lack of sufficient corpuscles to bring about the change.³⁹ The numerical lack of red blood cells would furnish a simple explanation of the decrease of the lipoids in the blood in a certain number of cases of anemia and would include all anemias due to any cause.

It is well known that the cholesterol in the blood increases in pernicious anemia when the patient improves. Wesselow⁴⁰ and Beck⁴¹ found a rough parallelism between the increase of erythrocytes and the cholesterol in the blood, the highest red blood cell count corresponding with the highest cholesterol values. However, an analysis of the relation of the concentration of red blood cells and hemoglobin to the amount of cholesterol in the blood revealed that no correlation existed.^{16, 17, 42} An analysis of 172 cases of pernicious anemia recorded in the literature⁴³ indicates that very variable results have been obtained even after allowance has been made for variations dependent upon technical methods. This variableness has been commented upon by Köhn.¹⁷ Many reports are inadequate. A great number of investigators report only one determination, often without recording count of the corpuscles or any other description of the stage of the disease. Thus in 120 out of 172 cases only one

cholesterol determination was made, 69 of which were accompanied with no data for red blood cells and hemoglobin.

The initial values in the 172 cases collected from the literature according to the standard of normal set by the respective authors were above normal in 18, normal in 47, and below normal in 107 or 62.2 per cent. Of the 101 cases, in which red blood cells are recorded, 21 cases had below 1 million per c.mm., 47 had between 1 and 2 millions per c.mm., and 21 between 2 and 3 millions per c.mm., while 11 had over 3 million red blood cells per c.mm. In the group with less than 1 million corpuscles per c.mm., 71.4 per cent had subnormal values for cholesterol, while in the group with between 1 and 2 million erythrocytes per c.mm., 61.7 per cent, and in the group with between 2 and 3 millions, 45.4 per cent had cholesterol values below normal. Thus only 54.7 per cent with a reduction of red blood cells and hemoglobin below 50 per cent of normal showed subnormal values for the blood cholesterol, while the remainder had normal or high values.

In view of the variableness of the results reported and the confusing picture obtained, it was thought worth while to restudy the relation of cholesterol, lecithin, and fatty acids in the blood plasma to the remission of pernicious anemia, and the changes brought about by various treatments calling forth a remission, especially in view of the greater control over the various phases of the disease that is offered by recent developments in therapy.

Procedure and Methods. Determinations of cholesterol, lecithin phosphorus and fatty acids in the plasma of 36 individuals have been made. Of these, 26 were undoubted and 8 doubtful cases of pernicious anemia, and 2 were healthy young males.

The examinations were carried out under as uniform conditions as possible so as to obtain comparative results. The blood as a rule was obtained at the same time every second day, in most instances over periods of weeks and in some instances during several months. The cholesterol and fatty acids were determined by Bloor's saponification method⁴⁴ and the lecithin phosphorus according to the method of Whitehorn,⁴⁵ both methods giving consistent values in duplicate. Brownish discolorations in the cholesterol determinations were obtained only exceptionally, and it was seldom marked enough to interfere with the readings. Citrated plasma was used as it has been shown³⁹ that the corpuscles in anemia as well as in other conditions tend to preserve a constant lipid composition, abnormalities being found mainly in the plasma.

The 26 cases of undoubted pernicious anemia have been divided for convenience in 3 groups, depending upon the severity of the anemia. These three groups include: (1) 6 patients with less than 1 million red blood cells per c.mm.; (2) 13 with between 1 and 2 million red blood cells per c.mm., and (3) 8 with above 2 million red blood cells per c.mm. This arbitrary division was made because

as a rule, the lower the red blood cell count the greater the rise of the reticulocytes in the peripheral blood.⁴⁶ It seemed of interest to attempt to correlate the reticulocyte rise to the lipoids of the blood.

The remissions of these pernicious anemia patients were called forth by various dietary procedures in conjunction with work done by Castle,⁴⁷ on the relation of achylia gastrica to the etiology of pernicious anemia, as well as by the addition of liver, liver extracts and kidney to the ordinary diet. A preliminary report of the work has been made.⁴⁸

GROUP 1. Of the 6 cases with less than 1 million red blood cells per c.mm., all showed low values for both cholesterol and lecithin, and 3 had even less than 50 per cent below normal.

Of these 6 cases 4 had a rapid remission, 1 died, and 1 remained in a stationary condition for about four months. The remissions were

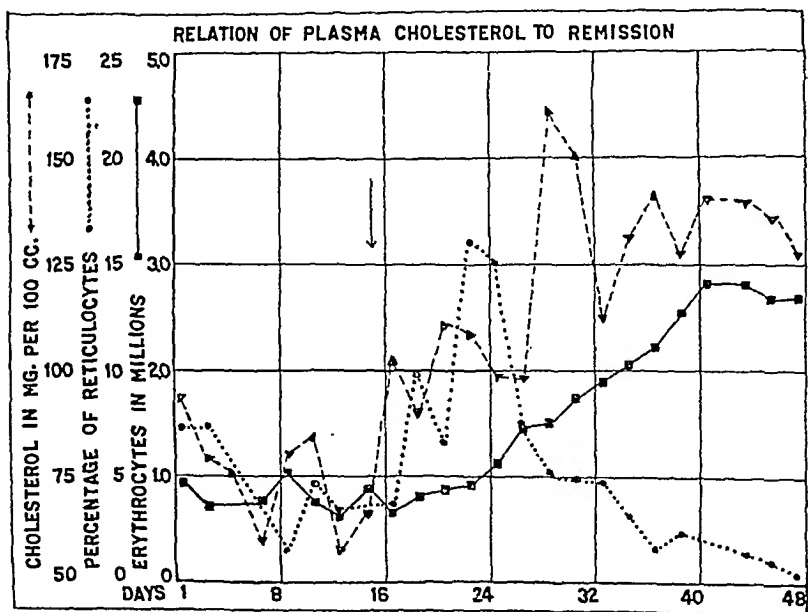


CHART I.—A case of pernicious anemia with erythrocytes below 1 million per c.mm. On the fifteenth day (note arrow) the reaction of the meat preparation was changed from pH 3 to 5.5.

called forth by feeding material rich in the active principle effective in pernicious anemia. The patient who died did so before proper treatment could be instituted, and the one whose condition remained stationary received no liver therapy.

The course of one of these cases is illustrated in Chart I. The diet was kept constant for the entire period, except that on the eighteenth day the pH of the meat that was fed after partial digestion with normal gastric juice was changed from 3 to 5.5. The chart shows that concomitant with the rise of the reticulocytes indicating the onset of remission, there was a sudden rise in the blood cholesterol, followed by small variations at the new level for about twelve days; then a secondary rise to a normal level took place which was main-

tained, as the reticulocytes gradually fell to normal values. The curve of the lecithin phosphorus followed the same general trend as that for the cholesterol, except that the secondary rise was not so marked. During the entire period the fatty acids varied within normal limits. Before the remission the fatty acid values were between 405 and 467 mg. per 100 cc. of plasma while after the remission commenced they varied from 384 to 491 mg. per 100 cc.

A second case with less than 1 million red blood cells per c.mm. during a nine-day control period was fed with an inert meat preparation. The course taken by the red blood cells, reticulocytes, cholesterol and lecithin phosphorus is illustrated in Table I. This table

TABLE I.—A PERNICIOUS ANEMIA PATIENT SHOWING RISE AFTER TRANSFUSION OF THE RED BLOOD CELLS WITHOUT INCREASE IN THE LIPOIDS. INCREASE OF CHOLESTEROL AND LECITHIN OCCURRED CONCOMITANT WITH THE ONSET OF REMISSION.

Days.	Red blood cells in millions.	Hemoglobin, per cent.	Reticulocytes, per cent.	Milligrams per 100 cc. of plasma.			Remarks.
				Cholesterol.	Lecithin.	Fatty acids.	
1	0.6	22	0.2	53	4.1	425	Predigested meat, 250-300 gm. daily. Gain of weight during period, 3½ pounds.
3	0.8	21	0.5	86	5.0	431	
5	0.6	19	0.6	91	4.7	469	
7	0.7	14	0.2	87	4.7	479	
9	0.6	15	0.1	48	3.9	419	
11	1.5	21	0.7	68	3.1	389	Transfusion, 500 cc. citrated blood. Experimental liver extract of moderate potency. No gain in weight.
13	1.2	17	1.0	71	4.2	426	
15	1.3	..	0.4	73	4.7	422	
17	1.5	..	6.0	79	4.4	437	
19	1.4	25	14.0	101	6.2	513	
21	1.6	..	3.3	110	6.5	586	
25	2.0	38	160	8.7	437	Raw liver pulp, 200 gm. daily. Gain of weight, 15 lbs. in one month.
27	1.8	38	151	6.1	498	
29	2.0	142	7.8	511	
31	2.8	51	142	8.1	465	
33	2.6	143	8.4	447	
38	3.6	53	150	7.9	476	

shows that the red blood cells remained about 700,000 per c.mm., while the cholesterol varied from 48 to 91 mg. per 100 cc. of plasma, and the lecithin phosphorus from 3.9 to 5 mg.; the lowest values being obtained on the ninth day when the patient was in a critical condition. A transfusion of 500 cc. of citrated blood was given and on the same day the patient was placed on a daily dose of potent liver extract. Following the transfusion the red blood cells rose from 600,000 to 1,500,000 per c.mm., without any appreciable rise of cholesterol or lecithin. On the sixth day after transfusion and the commencement of the administration of the liver extract,

remission set in as indicated by the rise of the reticulocytes, and the cholesterol had increased on the eighth day by about 40 per cent. This new level was maintained for six days, and then suddenly increased to normal values. Changes in the amount of lecithin phosphorus accompanied those of the cholesterol while the fatty acids during the entire period remained normal. The secondary increase of the cholesterol in this case was concomitant with a change from liver extract to raw liver. However, this increase of cholesterol was not due to cholesterol in the liver but to the administration of adequate amounts of the principle effective in pernicious anemia.

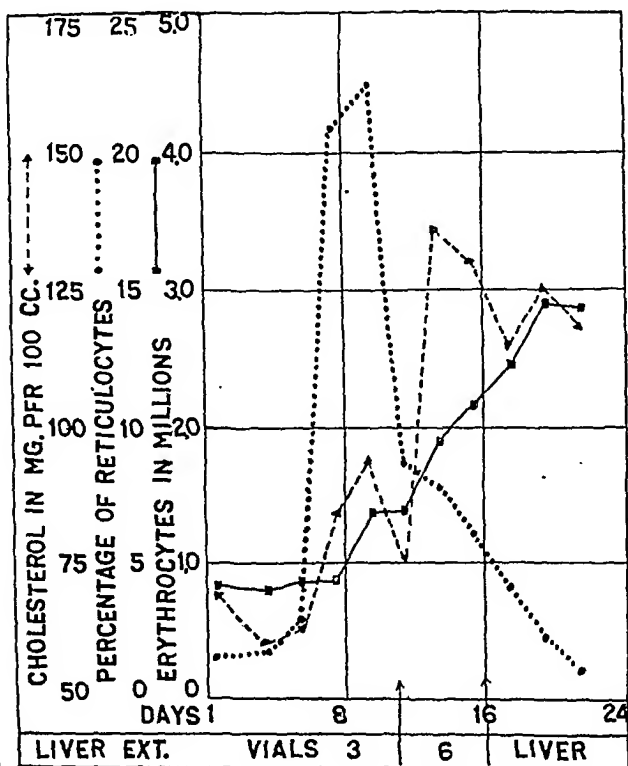


CHART II.—The effect of liver extract upon the plasma cholesterol in a case of pernicious anemia.

Note the moderate increase of the cholesterol with small doses of liver extract, the establishment of a normal level with larger doses, and the maintenance of the level when 240 gm. of broiled liver were fed daily. Each vial represents 100 gm. of liver of Liver Extract 343, N.N.R.

That liver feeding will not influence the content of the cholesterol and lecithin phosphorus in the plasma if unrelated to the remission as such, is illustrated in Chart II. This patient had 850,000 red blood cells per c.mm. before treatment. Liver Extract 343 (N.N.R.) derived from 300 gm. of liver was given daily for ten days. On the sixth day, reticulocytes commenced to rise. The cholesterol before remission varied between 60 and 70 mg. per 100 cc., then during the reticulocyte rise between 75 and 94 mg. On the

eleventh day the daily dose of liver extract was changed from that derived from 300 gm. to that derived from 600 gm. Two days later the cholesterol was 135 mg. per 100 cc., and remained at this normal level, without any further increase, when the patient was put on comparable amounts of whole liver. This indicates that a close relationship exists between the dosage of the principle effective in pernicious anemia and the rise of cholesterol in the plasma. The values of the lecithin phosphorus in this patient were not exceedingly low and the rise consequently not marked.

A fourth patient illustrates the influence on the lipoids of a remission which is not maintained, because of the withdrawal of the material initiating and maintaining the remission. During a control period of ten days the red blood cells and the cholesterol and lecithin declined. During this time the cholesterol gradually fell from 139 mg. per 100 cc. of plasma to 77 mg. The patient then was fed large doses of liver extract which caused a prompt onset of remission with a maximal reticulocyte response and a rise of cholesterol to 111 mg. when the red blood cells had risen only slightly. The liver extract was withdrawn and the patient put on a meat-free diet for twenty-four days. During this time, the patient gained weight (9 pounds) steadily and there was a slow gradual rise of the red blood cells and hemoglobin. During the first twenty days of this meat-free period the cholesterol fluctuated between 89 and 139 mg., it then rose to normal values without further change when steak was added to the diet. Four months later the patient had a severe relapse as the result of omitting treatment when again he showed a small amount of cholesterol and lecithin in the plasma. The response of the lipoids was typical at the onset of the remission, becoming increased before there developed any distinct increase of the red blood cells and later there followed a secondary rise to a normal level.

If the cholesterol and lecithin phosphorus are to show any increase, the change occurring in the organism and the hematopoietic organs which is designated as a remission must be real and lead to improvement. This is illustrated by the fifth case, with less than .1 million red blood cells per c.mm., which was followed for a period of four and a half months. This patient's blood count was increased from 900,000 to 1,800,000 per c.mm. by a transfusion of blood without any change in the lipoids of the blood. A remission due to feeding suboptimal doses of a material rich in the active principle effective in pernicious anemia with a reticulocyte count of only 16.9 per cent was frustrated by a change to an inert preparation and the red blood cell count remained stationary. With optimal doses at this low level of red blood cells, the reticulocyte response ought to have been about 35 per cent. The determinations made every second day were, respectively, 42, 32, 52, 73, 89 mg. per 100 cc. of plasma and the lecithin phosphorus rose from an average of 8 to 10 mg. per

100 cc. of plasma, without change in the level of fatty acids. This attempt of remission was not sustained and was not reflected in the increase of the erythrocytes and hemoglobin, illustrating convincingly that the cholesterol rises in proportion to the dose. This patient served for a long time to test materials and this was reflected in the cholesterol, which remained low during a four and a half month period, the values obtained varying between 32 to 98 mg. per 100 cc. of plasma. The lecithin phosphorus reached normal values at the time of the rise of the reticulocytes, then fluctuated between normal and values 50 per cent below normal.

In the sixth case, with a sudden fatal termination probably due to cerebral hemorrhage, the cholesterol remained low during one week's observation, while the lecithin phosphorus rose from 5.4 to 9.1 mg. per 100 cc. before death.

From these 6 cases, it may be concluded that the low values for cholesterol found in relapse change in an upward direction suddenly at the time remission begins, irrespective of the measures taken to establish a remission. The increase does not precede the reticulocyte rise but as a rule is concomitant with it, and occurs before any significant increase in the concentration of the red blood cells and hemoglobin. As far as can be determined from the data at hand the increase of cholesterol is not gradual but rises rapidly to a level somewhat below normal, remains there for a short interval, then shows a secondary rise to normal or to somewhat above normal. Transfusion of blood does not have any influence on the cholesterol content of the patient's blood. To obtain an increase of cholesterol and maintain the level a complete remission is usually necessary. A change in the form of effective therapy, as from liver extract to whole liver, causes no increase in cholesterol, indicating that the food as such has little or no influence in establishing the normal cholesterol level. The lecithin phosphorus fluctuates as a rule with the cholesterol although this was not observed in all cases. Practically normal values of the lecithin phosphorus may be observed with low values for cholesterol. The fatty acids in these patients varied within normal limits and no change in these constituents was seen at the onset of the remission.

GROUP 2. Twelve cases comprise this group of patients entering the hospital with a red blood cell count between 1 and 2 millions per c.mm. Eleven showed both a low cholesterol and lecithin content of the blood, while one had normal values. Five were treated with liver extract, and all promptly remitted. It is of interest to note that the case with the greatest concentration of reticulocytes at the peak of their rise had the cholesterol increase more promptly and of greater magnitude than the others. These cases illustrated the maintenance of the low level of cholesterol for long periods when inert preparations of meat or liver extract were tested and the rapid rise in remissions produced by adequate amounts of

potent material. In those cases fed suboptimal amounts of potent material the cholesterol tended to rise less abruptly and seemed somewhat delayed in exhibiting the secondary rise to a normal level.

This state of affairs is illustrated in Table II.

TABLE II.—A PERNICIOUS ANEMIA PATIENT WITH A FEEBLE RESPONSE DUE TO INADEQUATE LIVER THERAPY. THE CHOLESTEROL RISE IS LESS ABRUPT AND SOMEWHAT DELAYED IN REACHING A NORMAL LEVEL.

Days.	Red blood cells in millions.	Hemoglobin, per cent.	Reticulocytes, per cent.	Milligrams per 100 cc. of plasma.			Remarks.
				Cholesterol.	Lecithin.	Fatty acids.	
1	1.8	31	0.6	67	5.2	476	Experimental liver extract without potency.
5	1.3	26	65	8.2	437	
7	1.7	45	0.8	92	7.7	428	
9	1.6	..	4.0	98	9.3	395	
11	1.6	34	2.0	73	9.8	416	
13	1.6	..	2.4	93	8.7	451	
15	1.7	42	2.8	84	8.8	441	Liver Extract 343 N.N.R. derived from 300 gm. of liver.
17	1.6	40	1.1	107	6.4	421	
19	1.7	45	3.4	103	8.4	469	
21	1.7	42	6.4	123	10.8	386	
22	13.2				
23	1.8	42	120	10.7	355	
24	10.9				
25	2.0	51	5.6	118	9.4	400	
27	2.5	67	97	9.7	405	
29	2.5	76	103	9.8	416	
31	2.5	64	107	8.3	447	
35	2.8	79	144	11.1	438	
38	3.1	72	129	9.4	415	
42	3.2	74	136	9.5	441	Raw liver pulp, 250 gm. daily.
52	3.7	80	137	10.3	454	

Two of the patients deserve individual comments. A woman, aged seventy-one years, with 1.1 million erythrocytes per c.mm. and with 88 mg. of cholesterol and 3.7 mg. of lecithin phosphorus per 100 cc. of plasma was fed daily special prepared predigested meat. Determinations of the lipoids were done daily. For the first week, the red blood cells varied between 1 and 1.2 millions per c.mm., cholesterol between 77 and 96 mg., and lecithin phosphorus between 3.7 and 6.8 mg. per 100 cc. of plasma. During the following week a feeble irregular reticulocyte response was obtained with a maximum of 6 per cent. No appreciable rise of either cholesterol, lecithin phosphorus or red blood cells was observed during or after this abortive remission except that the fluctuations were over a slightly wider range. During a subsequent four weeks' period with the same treatment, the red blood cells varied between 0.9

and 1.6 millions per c.mm., the cholesterol between 89 and 116 mg. and the lecithin phosphorus from 6.2 to 9.6 mg. per 100 cc. of plasma. She was then fed 240 gm. of raw liver pulp. A remission set in promptly with a reticulocyte rise of small magnitude, reaching 8.7 per cent. The slight rise was dependent partially on the fact that a weak response had occurred before and infection complicated the picture. The cholesterol rose promptly to 136 mg., while the lecithin phosphorus fluctuated at the previous low level. A secondary rise of cholesterol to 156 mg. was accompanied by an increase of red blood cells from 1.4 to 2.1 millions per c.mm. without any definite increase in the lecithin phosphorus. The cholesterol level was maintained while the lecithin showed a gradual increase until high normal values were reached. The red blood cells and hemoglobin meanwhile reached normal values. The course taken by this patient's case presents a somewhat confused picture because of complications of bronchitis and cystitis. The remission was delayed but the outstanding feature is that the cholesterol rose promptly when finally the remission set in and the maintenance of the established level.

The second patient with an irregular course entered the hospital with low cholesterol and lecithin values and 1.6 million red blood cells per c.mm. This patient was observed for a period of eight months. The picture was complicated by a pyelitis, cholecystitis, cholelithiasis, and fever during the first month. A remission on a meat preparation was accompanied by a slight increase of the cholesterol level from between 61 and 72 mg. per 100 cc. of plasma to a level between 83 and 104 mg. per 100 cc. during the reticulocyte rise, and an increase of the lecithin phosphorus from a level varying between 5.2 and 6.7 mg. to a level between 5.6 and 8 mg. per 100 cc. of plasma. The remission was not maintained because of obvious inadequate therapy, and a transfusion of blood was given and liver extract administered but not in maximal doses. A second rise of reticulocytes to 15.2 per cent indicated a response but the number of red blood cells remained practically stationary for a period of forty-two days because of infection and insufficient supply of active principle. The average of 18 cholesterol determinations during the period was 81 mg. with a maximum of 125 mg. per 100 cc. of plasma, and a subsequent minimum of 48 mg. per 100 cc. After the infection had subsided, the red blood cells increased slightly with the establishment of a higher level of cholesterol to an average of 104 mg. per 100 cc. Permanent improvement did not occur until optimal doses of potent material were fed. This was accompanied by a further rise of cholesterol to a higher level. The lecithin phosphorus during the second reticulocyte rise increased from an average of 7.1 mg. before to 10 mg. per 100 cc. during the reticulocyte rise, subsequently to decline somewhat, fluctuating between 7.1 and 10 mg. per 100 cc. The fatty acids during this period showed no

definite trend, varying within normal limits during the entire period of observation.

Of the remaining 4 patients with red blood cells between 1 and 2 million per c.mm., entering the hospital in relapse, one obtained a typical although less pronounced rise of cholesterol and lecithin at the time of remission provoked by a test preparation of meat, while another showed a sudden rise of cholesterol late in the remission as indicated by the reticulocyte curve, which rose to 11.6 per cent but tended to be long drawn out. The lecithin rose at the beginning of the remission. A third patient had a remission without specific treatment with a typical increase of cholesterol, while the fourth, observed for three months, also had a spontaneous reticulocyte rise. This latter patient showed low cholesterol value during the entire period. The highest value obtained was 118 mg. per 100 cc. just before the increase of the reticulocytes when the red blood cells were 1 million per c.mm., then declined to a value of 0.073 per cent with 2.9 million erythrocytes per c.mm.

The last case in this group entered the hospital with 1.9 million cells per c.mm. and 170 mg. of cholesterol per 100 cc. of plasma. The red blood cells increased gradually to 4.5 million cells per c.mm., without any change of cholesterol or lecithin phosphorus from the variation of a high normal level. The reticulocytes numbered 7.4 per cent on the day after admission so that one may conclude that a remission had commenced when he entered the hospital.

GROUP 3. The third group of pernicious anemia cases, 8 in number, had red blood cell counts over 2 million per c.mm. They showed greater variations both in the clinical picture as well as in the course of the lipoids of the blood than the cases comprising Groups 1 and 2. Only 2 of the 8 cases had low cholesterol and lecithin values. One recovered promptly on a kidney diet, with a rise of red blood cells from 3.4 to 4.5 millions per c.mm., without any appreciable rise in reticulocytes, as at this level of red blood cells the reticulocyte response is usually slight, but with a sudden rise of cholesterol from a level below 75 mg. to 146 mg. per 100 cc. of plasma. Nine days later a still higher level was established and this was maintained. The other patient with a low plasma cholesterol at first had a decline of his red blood cells, plasma cholesterol and lecithin phosphorus, then as remission commenced there was a typical rise of cholesterol, while the lecithin phosphorus remained at a comparatively low level for a considerable period, first reaching a normal level when the red blood cells approached 4 millions per c.mm.

Five patients of this group entered the hospital with a moderate anemia and normal levels of cholesterol and lecithin phosphorus in the blood. Dietary procedures that were instituted which can induce remissions were without appreciable influence on the lipoids of the blood. One of these patients reentered the hospital six

months later with 3.3 million red blood cells per c.mm., and lower values for cholesterol and lecithin phosphorus than on the previous admission. At this time for one month the cholesterol fluctuated back and forth between 104 and 150 mg. per 100 cc. of plasma and the lecithin phosphorus between 7 to 10.4 mg. per 100 cc., although the erythrocytes rose to 4 millions per c.mm., as the result of the feeding of a test preparation of meat partially digested by normal gastric juice. The red blood cells rose from 4 to 4.6 millions per c.mm. when liver extract was administered and the level of cholesterol became fixed between 143 to 163 mg., and lecithin phosphorus between 8.5 to 12.2 mg. per 100 cc. of plasma during the following four months.

The last case in this group was atypical in that the cholesterol remained at a comparatively low level during the time of observation. The erythrocytes on admission were 2.4 millions per c.mm. The patient was fed daily about 200 gm. of kidney. During a twenty-five-day period the red blood cells rose to 3.4 millions per c.mm., without any increase of the reticulocytes. The cholesterol during this same time varied between 96 and 129 mg. per 100 cc. of plasma with an average of 8 determinations of 115 mg. The lecithin phosphorus averaged 7.8 mg. per 100 cc. of plasma with a minimum of 6.7 and a maximum of 9.7 mg.

Lipoids in Pernicious Anemia Before Definite Relapse. Seven cases diagnosed as early or doubtful pernicious anemia were studied. All of them showed an anemia of slight degree. Three had a plasma cholesterol at the upper limit of normal, 2 had an average normal amount, while 2 showed low cholesterol values. One of the latter with a red blood cell count of 4.1 millions per c.mm. had cholesterol values between 76 to 103 mg., and lecithin phosphorus between 9.1 to 10.4 mg. per 100 cc. of plasma, while the other had a range of red blood cells over a month's period (13 determinations) of 3.6 to 4.7 million red blood cells per c.mm. The cholesterol varied between 98 and 126 mg., and the lecithin phosphorus from 8.3 to 11.1 mg. per 100 cc. of plasma. Thus, in these 2 cases, which were not treated with liver or a potent substitute, the cholesterol was low, and remained so without any tendency to increase, while lecithin varied within normal limits.

Lipoids in Normal Adults Fed Liver and Liver Extract. Two healthy male individuals were studied in addition to the cases of pernicious anemia. Daily cholesterol, lecithin phosphorus and fatty acid determinations were made. For the blood counts I am indebted to Drs. W. C. Townsend and G. R. Robb. The lipid determinations were made on the same specimen of venous blood used for the blood counts. In addition three daily red blood cell counts were made on the capillary blood. The counts obtained from both the venous and the capillary blood showed practically identical values. The reticulocytes remained at a normal level.

The daily variation in red blood cells, cholesterol, lecithin phosphorus and fatty acids is illustrated in Chart III.

From an examination of the graphs which are entirely comparable for both individuals, it is evident that neither optimal amounts of liver nor liver extract for pernicious anemia patients cause in the normal person a change in the level of the red blood cells or the lipoids. The average of the cholesterol in one case was 132 mg. per 100 cc. of plasma with a minimum of 121 mg. and a maximum of 156 mg., while the average of the other was 155 mg. per 100 cc. of plasma with a minimum of 139 and a maximum of 175 mg.

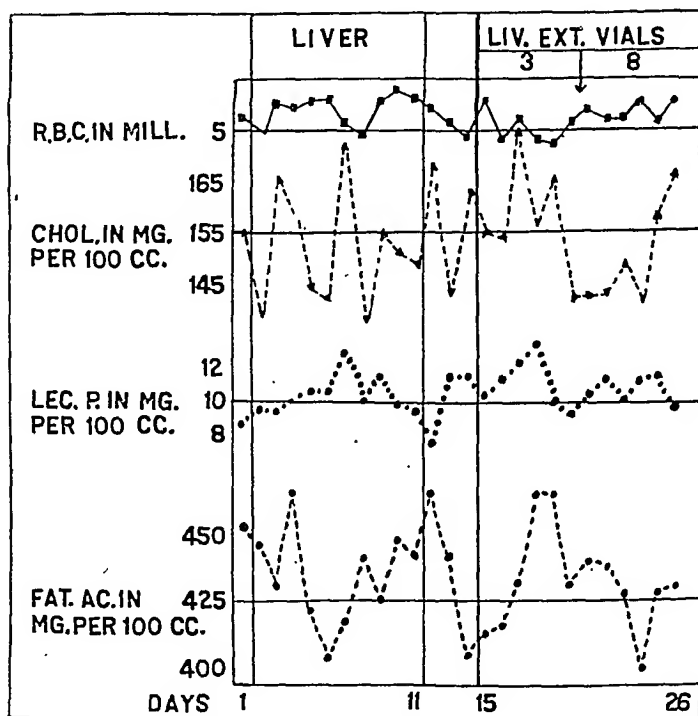


CHART III.—The variation of red blood cells, cholesterol, lecithin phosphorus and fatty acids in a healthy adult male, with liver and liver extract added to the diet.

The amount of liver fed was gradually increased from 200 to 300 gm. Each vial of liver extract represents 100 gm. of Liver Extract 343, N.N.R. Neither liver nor liver extract was administered on the first day or between the eleventh and fifteenth days.

Discussion. The findings in this series of cases of pernicious anemia show that the cholesterol in the blood plasma is low in relapse but that a sudden rise to a higher level, which later increases and is maintained, occurs at the onset of the remission. The increase of the cholesterol, as a rule, is concomitant with the reticulocyte response and apparently proportional to the intensity of this reaction. The increase of the cholesterol is not dependent upon whether the active principle effective in pernicious anemia is fed in one form or another, nor upon the number of red blood cells in the peripheral blood, but upon the change that takes place in the organism at the onset of a remission. It is, however, proportional to the amount fed

of the active principle effective in pernicious anemia. Suboptimal doses call forth an irregular response of the cholesterol, while optimal doses increase and maintain the cholesterol at a normal or high level. As in the case of the reticulocytes, the response of the cholesterol is of greater magnitude the lower the red blood cell count. After the remission has commenced, a change from liver extract to liver, kidney or meat, partially digested with gastric juice, which contain a considerable amount of cholesterol does not influence the level of cholesterol except when the remission has been weak because of inadequate dosage and the cholesterol level has been fluctuating within wide limits. In such cases, the administration of adequate doses of the effective principle caused the level to become steady at normal figures.

An incomplete response of the reticulocytes without actual improvement in the patient calls forth a slight increase in the cholesterol temporarily with a subsequent fall to the previous level. Infection, delaying or giving an irregular response to treatment, like inadequate dosage, is reflected in an irregular cholesterol and lecithin phosphorus curve with wide fluctuations.

In healthy individuals, the administration of large doses of liver and liver extract does not cause an appreciable change of the level of cholesterol. From the examination of Chart III it is evident that moderate daily fluctuation occurs in the cholesterol level. Thus by establishing the relation of the cholesterol to the onset of remission in pernicious anemia a probable explanation, at least, in this disease, has been obtained for the apparent lack of correlation of the cholesterol to the severity of the anemia. Normal or high values for plasma cholesterol with low red blood cell counts in pernicious anemia indicate that remission is taking place.

Recent reports from Germany confirm the above observations. Adler and Schiff¹⁹ found that the cholesterol in the blood of pernicious anemia patients increased in quite the same way when liver extract or raw liver was fed. Contrary to the observations recorded here, they found an increase of plasma cholesterol in healthy persons partaking of a liver diet. In animals, Adler and Schiff noted that "hepatrat," a liver concentrate, as well as whole liver, increased the blood cholesterol but the bile cholesterol did not vary after the administration of either the extract or whole liver. Consequently these authors concluded that the increase of cholesterol in the blood after administration of liver and liver extract was not due to an alimentary hypercholesteremia but depended upon the intermediary metabolism. The same conclusion was drawn by Wesselow.⁴⁰ Beck⁴¹ found that in patients whose erythrocyte count was not influenced, the cholesterol content of the blood did not change. That a high fat meal does not increase the cholesterol in the blood in pernicious anemia has been shown by Broun⁴⁹ who examined 4 patients at frequent intervals during eight hours after a high fat meal.

Very few facts are available to adequately explain the low values of cholesterol in pernicious anemia and the sudden change at the onset of remission. The blood volume in pernicious anemia is usually reduced⁵⁰ while the plasma volume remains essentially normal. Wesselow⁴⁰ observed that the absolute plasma volume showed a considerable degree of constancy during the progress of treatment with liver, with a slight tendency to fall during the later stages of improvement.

In most cases of pernicious anemia, digestive disturbances are present. Nevertheless, Kahn and Barsky⁵¹ and Gibson and Howard²⁵ found a normal fat content of the stools. Cornell⁵² came to the conclusion that there is no evidence of abnormal metabolism of simple fats and a satisfactory usage of fat although there is a tendency to overstorage and pathologic infiltration by fat in active tissues. The relation of frequent and loose stools to the cholesterol content of the blood has been investigated by Schnabel.³⁶ In 3 cases given no other diagnosis than diarrhea he found high normal values, while patients with achylia gastrica had cholesterol within normal limits.

However, in pernicious anemia Reicher⁵³ found an increase of cholesterol in the stools. In a patient with pernicious anemia in a four-day control period a daily average of 0.6333 gm. of cholesterol was excreted, while after a daily addition of 3 gm. of cholesterol to the diet in an eight-day period, only an average of 0.5484 gm. was excreted, indicating a retention. In this connection, it is of interest to note that Reicher reported improvement in pernicious anemia after administration of cholesterol. In a control patient with mitral insufficiency, the daily average during a control period was 0.2908 gm., while the addition of 3 gm. of cholesterol increased the average daily output over a four-day period to 2.0766 gm.

In cholesterol-balance experiments on 3 pernicious anemia patients, Beumer⁵⁴ found a negative balance in each case of 0.025, 0.119, and 0.207 gm. respectively. A healthy person showed a negative cholesterol balance over a ten-day period of 0.081 gm. Normally a negative balance of cholesterol is present in man, but no conclusion can be drawn from the above results in pernicious anemia as no data are given to indicate the condition of the patients, except that they were "at a standstill showing no progress." This is realized by Beumer, who states that the remission, crisis or a stationary condition may influence cholesterol metabolism. On the other hand, in nephrosis, Beumer⁵⁴ demonstrated a retention. This is of interest as in nephrosis the cholesterol in the blood is increased.

Loss of cholesterol in the stools has been reported by Rosenbloom and McKelvy⁵⁵ in a patient with hemolytic icterus. A diet containing 5.22 gm. of cholesterol, determined by the method of Windaus, was given. The cholesterol obtained in the feces was 12.27 gm., giving a negative balance of 7.05 gm.

Barat⁵⁶ demonstrated in 5 cases of pernicious anemia that the cholesterol in the bile was greatly increased. Rosenthal⁵⁷ explains the decrease of cholesterol in the blood in hemolytic jaundice and pernicious anemia as probably due to the loss of cholesterol through the bile. As a rule, blood cholesterol in hemolytic jaundice is low.

Very few data are available on the blood lecithin of pernicious anemia. Beumer and Bürger,⁵⁸ in 1913, found low values. Bloor and MacPherson³⁹ in 7 pernicious anemia patients found values for lecithin at the lower normal limit or below normal. In the plasma of 3 cases in which the number of corpuscles was low, there were constantly low values for lecithin, while in a fatal case the lecithin increased in the plasma as the number of corpuscles diminished. The same was observed in one case in this series. Feigl⁵⁹ reported a study of 17 cases of pernicious anemia patients with determinations of the fatty acids, lecithin and cholesterol in the blood plasma. Twenty-four determinations are recorded. Low lecithin values were found in 7 patients and above normal in one. The rest were within normal limits. In the patient, with high lecithin values, the cholesterol and fatty acids were also high with a red blood cell count of 400,000 per c.mm., and 10 per cent hemoglobin. In all the cases with low lecithin values the cholesterol was correspondingly decreased, although a normal amount of lecithin was present with subnormal cholesterol in one case. The fatty acids were increased in 10 patients, below normal in 2, and normal in 5. No correlation could be established between the level of the erythrocytes and hemoglobin on the one hand and the lipoids on the other. The 3 patients with the lowest red blood cell counts showed fatty acids below normal, normal and above normal. Bloor and MacPherson³⁹ could not verify the abnormally high figures for fat in the blood of pernicious anemia patients reported by King.⁶⁰ They found the fatty acids to be within normal limits while total fat was increased. Marked abnormalities were found mainly in the plasma, the corpuscles in anemia as in most other conditions tending to preserve a constant lipid composition. The relationship of fatty acids, lecithin and cholesterol to each other in the plasma and corpuscles has been reviewed by Bloor.²⁰ In lipemia⁶¹ the increase of cholesterol and lecithin follows rather closely the increase of fat, but the values of cholesterol and lecithin remain high after the fat has decreased to normal and falls to normal only after several days. This slower rate of removal of lecithin and cholesterol as compared with fats points to a different mechanism for the removal of the two groups of lipoids.

In the present study the lecithin phosphorus followed the cholesterol closely in many instances, being low in the relapse of pernicious anemia and increasing suddenly at the onset of remission. In other cases the lecithin was within normal limits when low cholesterol values were found. In all cases no significant change was

observed in the fatty acids, the same fluctuations being observed both before and during and while in remission. The sudden rise in the lecithin, before any appreciable increase of red blood cells makes one question in how far the number of red blood cells in the peripheral blood regulates the level of the lecithin phosphorus in the plasma.

A few suggestive reports on the relation of the lipoids to cell proliferation ought to be cited. Cholesterol^{62, 63} has been claimed as an agent that can increase the growth of cells while lecithin retards growth of carcinoma cells.⁶³ On the other hand, Masing⁶⁴ suggested the use of the phosphorus content of the erythrocytes as a criterion of the presence of newly formed red blood cells. A higher percentage would indicate a stimulation of the erythropoietic organs. Young red blood cells as well as immature white blood cells contain more phosphorus than mature cells.^{65, 66} Bloor⁶⁷ found an increase of lipid phosphorus in the young red blood cells of rabbits after bleeding, but whether this increase was characteristic of young erythrocytes or due to the lipemia he was not prepared to say.

An interesting experiment has been reported by Sundstroem and Bloor.⁶⁸ In animals subjected to low barometric pressure experimentally the lipid phosphorus decreased on an average 13.2 per cent when compared with the constancy of the lipid phosphorus in controls (average 1.6 per cent). These figures led the authors to conclude that the decrease of the lipid phosphorus is due to the low oxygen tension, as digestion and work were excluded. The enrichment of the circulating red blood cells with lipoids, that would result in impoverishment of these substances in the plasma did not occur, as it was found that the greatest decrease in plasma lipoids was accompanied by a proportional decrease of corpuscle lipoids. Sundstroem and Bloor thought that the phospholipoid was deposited in the hematopoietic organs, as elimination through the kidney was excluded, and the plasma volume was concentrated rather than diluted. It has been shown that lecithin plays some rôle in erythropoiesis since the bone marrow contains comparatively large amounts and it is higher in the red marrow of the young than the aged.⁶⁹ The enrichment of the erythropoietic organs with lipid material, Sundstroem and Bloor suggested might be the first phase of a stimulation of these organs resulting from a lowering of the atmospheric pressure.

Some evidence that also cholesterol is retained and perhaps deposited in a hyperplastic bone marrow has been given by Rewald.⁷⁰ He examined the femoral bone marrow for cholesterol in one case of pernicious anemia. He found the water content enormously increased and the dry substance correspondingly decreased, but in spite of this the cholesterol in the dried substance was not decreased constituting 0.9288 per cent as against 0.6550 per cent in a patient

who died from lysol poisoning. The possibility of the utilization of the lipoids in the formation of the enormous number of megaloblasts in the bone marrow in pernicious anemia must be thought of. The extent of this new formation is realized when it is considered that the bone marrow, the full potential capacity of which is realized in pernicious anemia, is inferior in weight only to the skeleton, muscles and blood.⁷¹ For each gram of blood there is 0.55 gm. of bone marrow.

The cholesterol and other lipid content of various organs in pernicious anemia has been reported increased by some^{72, 73} while others have found decreased values.^{74, 75} Piney⁷⁶ states that in pernicious anemia the liberation of lipoids from the destruction of red blood cells is probably the direct cause of the intense fatty changes found in the liver, heart and other organs. He considers that the normal mechanism for storage of fat is stimulated.

In a review⁴³ of the relation of the reticuloendothelial system to cholesterol metabolism, it was found that hypocholesteremia can be produced by the stimulation of this system with colloidal substances. Cornell⁵² reflecting on the various data brought out by recent work suggests the possibility that in pernicious anemia the total hematological manifestation may result from abnormal cell metabolism on the part of the reticuloendothelial system. There is suggestive evidence that cholesterol excretion and perhaps also the deposit in the tissues are increased, and that both cholesterol and lecithin may participate in the formation of new red blood cells. Whether there is a decrease of the elimination of cholesterol through the bile and the feces at the onset of remission is unknown. There exist no data concerning the excretion and balance of cholesterol at this stage of the disease.

The elucidation of what actually occurs in the patient with pernicious anemia at the onset of remission and during its progress will bring forth valuable information not only as to the disease pernicious anemia but also as to the regulatory mechanism of cholesterol and lecithin within the body.

Conclusions. 1. Cholesterol, lecithin phosphorus and fatty acids of the blood have been determined at frequent intervals in 26 cases of pernicious anemia, especially with reference to the remission. Eight early or doubtful cases of pernicious anemia and 2 normal adults have been studied in like manner.

2. In pernicious anemia in relapse the cholesterol and lecithin phosphorus are low, while the fatty acids show variations apparently within normal limits.

3. In typical cases of pernicious anemia in marked relapse the cholesterol rises suddenly at the onset of the remission. The rise is concomitant with the response of the reticulocytes and as a rule is proportional to the intensity of the remission and of greater magnitude the lower the red blood cell count.

4. The increase of cholesterol occurs before there is a definite increase in the concentration of erythrocytes and hemoglobin. It is independent of transfusion of blood and is called forth by an adequate dose of potent material effective for pernicious anemia. The results are the same no matter whether the potent material is fed in the form of liver, kidney, liver extracts, or certain preparations of meat partially digested with normal gastric juice. Thus the increase is associated with the induction of remission.

5. In cases fed suboptimal amounts of potent material effective in pernicious anemia the cholesterol level showed wide fluctuations, but when addition of optimal amounts was made there occurred a prompt decrease in the fluctuations and such dosage then maintained the cholesterol at a normal level. In abortive remissions there is a slight rise of cholesterol at the time of the incomplete response of the reticulocytes with a return to the previous low level. To obtain a normal level of cholesterol a satisfactory type of remission is necessary.

6. After the rise of cholesterol, the increase red blood cells is not followed by a proportional increase of cholesterol although in individual cases values above normal may be obtained.

7. Infection, when delaying or causing an irregular remission, is reflected in an irregular response of the lipoids of the blood.

8. The lecithin phosphorus as a rule follows the cholesterol, although exceptions occur. Occasionally normal values of lecithin are found with subnormal values of cholesterol or the lecithin phosphorus may rise somewhat more slowly.

9. The fatty acids do not show any significant variation during remission, the same fluctuations around a normal level being obtained before and after the onset of remission.

10. In early or doubtful cases of pernicious anemia with a slight anemia, the level of cholesterol may be high or normal and occasionally somewhat lower than normal.

11. In two healthy men, studied over a considerable period, the addition of liver or liver extract to the diet did not influence the level of cholesterol, lecithin phosphorus, fatty acids or number of erythrocytes and reticulocytes.

12. It appears that the low cholesterol and lecithin phosphorus content of the plasma in complete relapse of pernicious anemia is dependent on the disease process and that the establishment of a normal level of the lipoids is closely associated with the onset of remission or the change that occurs when the reticulocytes respond to therapy and when there is a decrease of bilirubin in the plasma and sudden improvement of the patient. The elucidation of the cause of these changes will throw light on the regulatory mechanism of lecithin and especially cholesterol.

13. The total inconsistency of the reports in the literature concerning the relation between the blood cholesterol in pernicious

anemia, and the concentration of the erythrocytes and hemoglobin, is explained by the results recorded. Normal or even high values may be present with severe anemia, provided remission has begun.

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PAROXYSMAL VENTRICULAR TACHYCARDIA.

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PAROXYSMAL ventricular tachycardia has been described now for twenty years. Although case reports have been more frequent recently, only 65 undoubted cases could be found in the literature to this time. It is the purpose of this paper to summarize some of

the data of these cases and to add 2 cases, 1 studied with regard to the control of the rapid rate, the other exhibiting bidirectional electrocardiograms.

Definition. Paroxysmal ventricular tachycardia can be recognized definitely only by means of the electrocardiograph, although certain clinical signs make the diagnosis probable. With the electrocardiograph, several criteria, originally outlined by Robinson and Herrmann,¹ are necessary for the diagnosis. There must be evidence that the impulses producing the tachycardia arise within the ventricles, in which case the form of the *Q-R-S* complexes will be distinctly abnormal. This abnormal form, however, cannot be taken as pathognomonic, as it occurs in cases of bundle-branch block and in cases of simple auricular tachycardia (White and Stevens,² Lewis,³ Marvin and White⁴). The identification of independent auricular waves, occurring at a slower rate than the ventricular waves, is in favor of a ventricular origin of the tachycardia. If in the interval between paroxysms the ventricular complexes are normal and there are isolated premature ventricular complexes of the same shape as those of the paroxysm, the diagnosis can be made certain. Additional evidence may be obtained by observing that the onset and offset of the tachycardia bear the same relation to the slow rate as do isolated premature systoles, and that there is a slight irregularity in the rapid rate, noted by Strong and Levine,⁵ which is not to be found in other forms of paroxysmal tachycardia.

Experimental Ventricular Tachycardia. Lewis has produced paroxysms of tachycardia of ventricular origin in both dogs and cats by the ligation of a coronary artery, particularly the right coronary,⁶ and with Levy has shown that the same effect may be produced by the combination of intravenous adrenalin and the inhalation of varying tensions of chloroform vapor.⁷ Rothberger and Winterberg have found that after sensitization of ventricular foci of impulse formation with barium chlorid, either direct stimulation of the accelerator nerves or adrenalin will produce a ventricular tachycardia.⁸ Gold was unable to produce this irregularity by the use of digitalis following ligation of a coronary artery in cats.⁹

Clinical Ventricular Tachycardia. Since Lewis' first 2 cases,¹⁰ 63 additional cases have been described in the literature.^{1,4,5,11-38} Half that number of cases have also been recorded in which entirely adequate diagnostic criteria were not present, although many are probably true cases of the arrhythmia.^{5,10,13,14,17,18,24,39-49} Clinical history was available in 64 undoubted cases, including the 2 cases presented below.

Age Incidence. This is shown graphically in Fig. 1. Sixty per cent of the cases occurred during the fifth and sixth decades, 14 per cent before this period and 26 per cent later in life.

Sex Incidence. Forty-three, or slightly over two-thirds of all the cases occurred in members of the male sex.

Morphologic Pathology. In 11 of the 64 cases there was no clinical or laboratory evidence of pathology other than the arrhythmia. The remaining 53 cases all presented evidence of cardiac pathology:

Type of heart disease.	Number of cases.
Cardiovascular-hypertensive disease	16
Coronary disease	12
Rheumatic heart disease	8
Arteriosclerotic heart disease	4
Syphilitic heart disease	4
Thyreotoxic heart disease	2
Type of heart disease not clear	7

Functional Pathology. Heart failure, either of the congestive or anginal type, was present when the tachycardia was first noted in 45 instances. Auricular fibrillation was present in 21 cases and auricular flutter in 2.

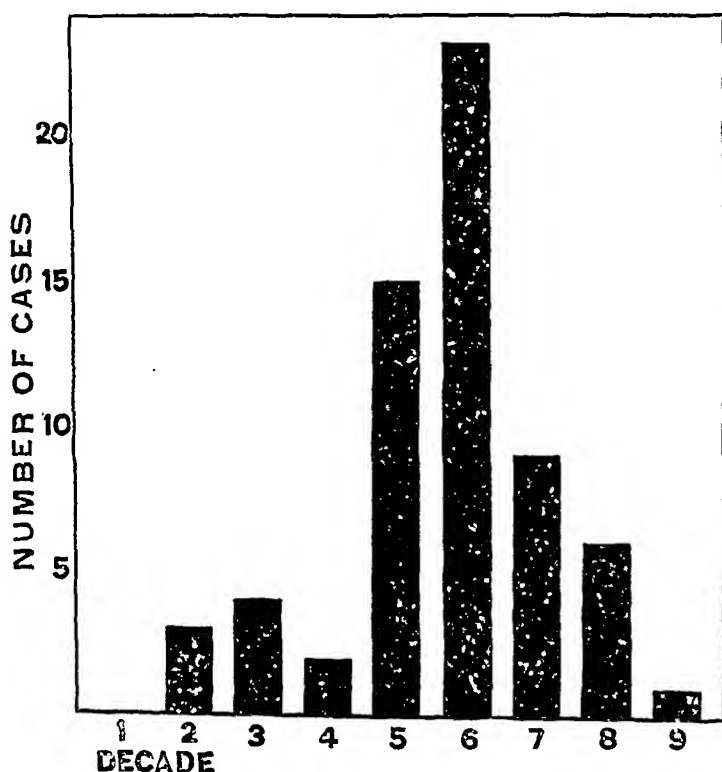


FIG. 1.—Age incidence by decades of paroxysmal ventricular tachycardia.

Digitalis had been administered before the onset of the tachycardia to 50 per cent of the cases, all in the group presenting definite cardiac disease. In some cases the dosage was excessive, while in others it was entirely too small to produce any effect. In a number of cases the withdrawal of digitalis was followed by a cessation of the tachycardia, while its subsequent use resulted in a return of the rapid rate, indicating that in the presence of organic heart damage

this arrhythmia may be one of the toxic manifestations of digitalis administration.

When the electrocardiograms are of the usual type (Fig. 3) most writers have considered that a single irritable ectopic ventricular focus has been the mechanism responsible for the tachycardia. In 18 of the 64 cases bidirectional alternation of the complexes occurred^{16,18,22,24,26,29,33,34,36,37} similar to that in the second lead of Fig. 2. Alternate blocking of the left and right branches of the conduction system, at first suggested as the mechanism of this condition, with a single focus of stimulus production, seems unlikely. Multiple foci of impulse formation or circus movements in the ventricle similar to those in the auricle in auricular fibrillation and flutter have been given most emphasis in the recent excellent discussions of Palmer and White³³ and Marvin.³⁷

Clinical Diagnosis. Suspicion of the presence of paroxysmal ventricular tachycardia must be aroused whenever a rapid, almost or completely regular, rate supervenes in a case of long-standing heart disease, particularly if large doses of digitalis have been used, or in a case of coronary occlusion. Levine and his co-workers^{5,38,50} have emphasized certain aids to bedside recognition. There is a slight irregularity, frequently noted in auscultation, which is found in tachycardia of ventricular origin, not to be found in other forms. At the same time the quality of the first heart sound may perceptibly vary in different cycles. Vagal stimulation and ocular pressure are never effective in terminating a paroxysm of ventricular tachycardia, thereby offering a third differential measure. Positive diagnosis can only be made by the electrocardiograph.

Treatment. Only one therapeutic measure has been successfully employed in terminating ventricular tachycardia—quinidin, usually used as the sulphate. Paroxysms were controlled in all 16 cases in which it was employed.^{15,17,20,21,23,25,27,28,29,30,32,35,38} Doses as high as 7.5 gm. a day have been utilized, while maintenance has been sometimes possible on as low as 0.2 gm. per day. Dosage must be adjusted to the individual case, repeating the administration in increasing amounts every few hours, until the paroxysm is controlled or alarming symptoms appear. Although this may seem dangerous therapy, no bad effects have been recorded due to the drug in this condition, and in many cases in which the rapid rate was quickly producing myocardial exhaustion, the use of it has been life-saving. It is interesting to note that in the older literature on quinidin in the treatment of auricular fibrillation, the possibility of ventricular tachycardia or fibrillation was mentioned. One such case exists in our records, in which the withdrawal of quinidin resulted in a termination of the tachycardia. This paradoxical action has not been adequately explained.

Prognosis. Of the 11 cases showing no pathology other than the arrhythmia, all were living at the time of publication of the reports,

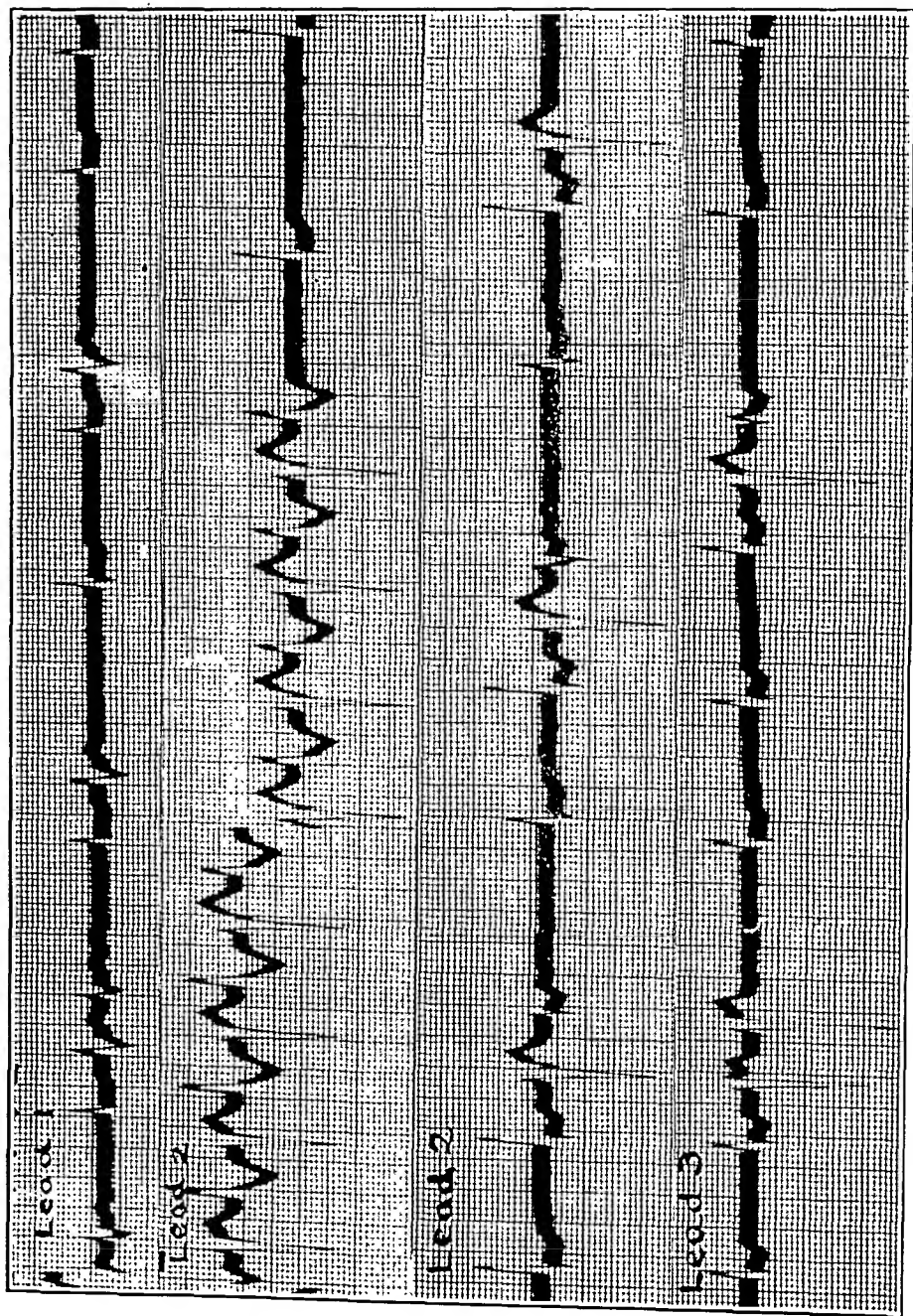


FIG. 2.—Case I. July 2. Premature ventricular systoles, Leads 1, 2 and 3. Paroxysm of ventricular tachycardia showing bidirectional alternation, Lead 2.

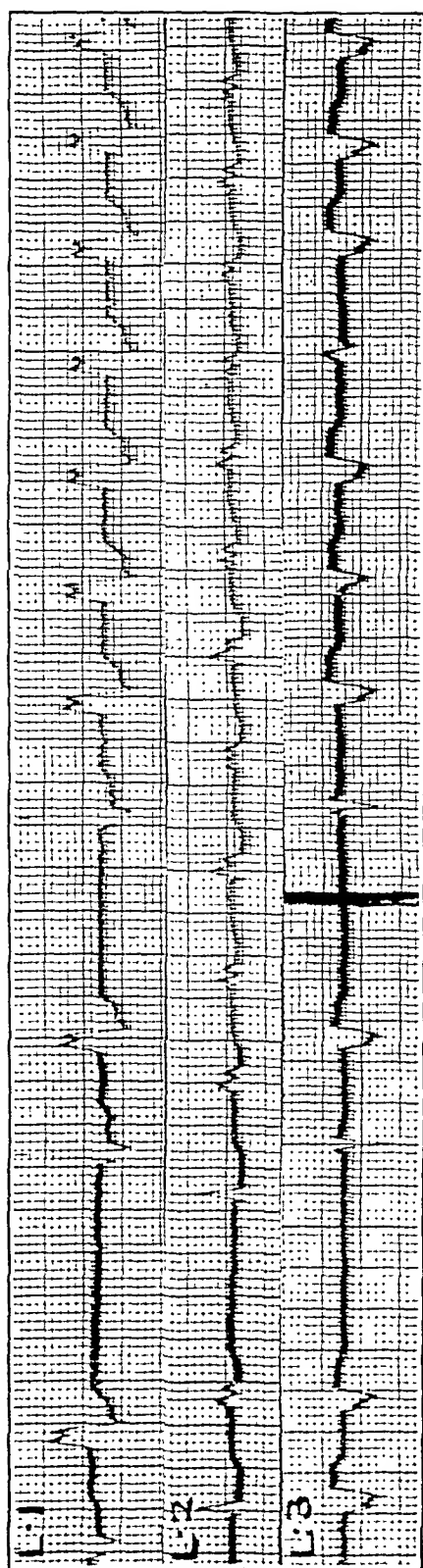


FIG. 3.—Case II. September 25. Paroxysms of ventricular tachycardia and bigeminy, Leads 1, 2 and 3.

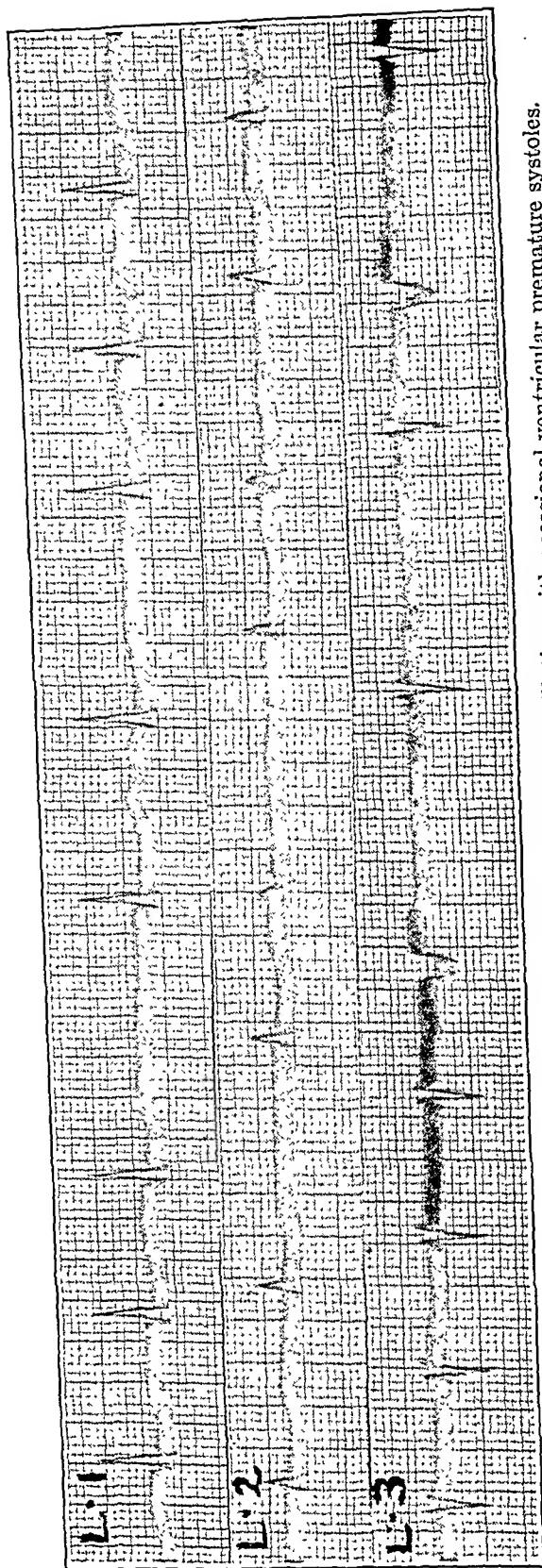


FIG. 4. --Case II. October 8. Quinidin, 1.2 gm. daily. Auricular fibrillation with occasional ventricular premature systoles.

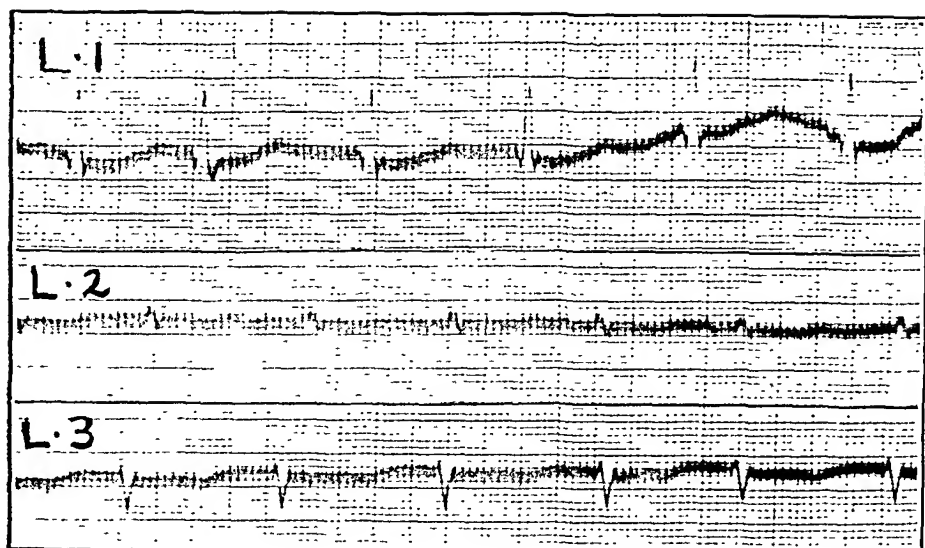


FIG. 5.—Case II. October 10. Quinidin, 1.6 gm. daily. Very slow fibrillation.
No premature systoles.

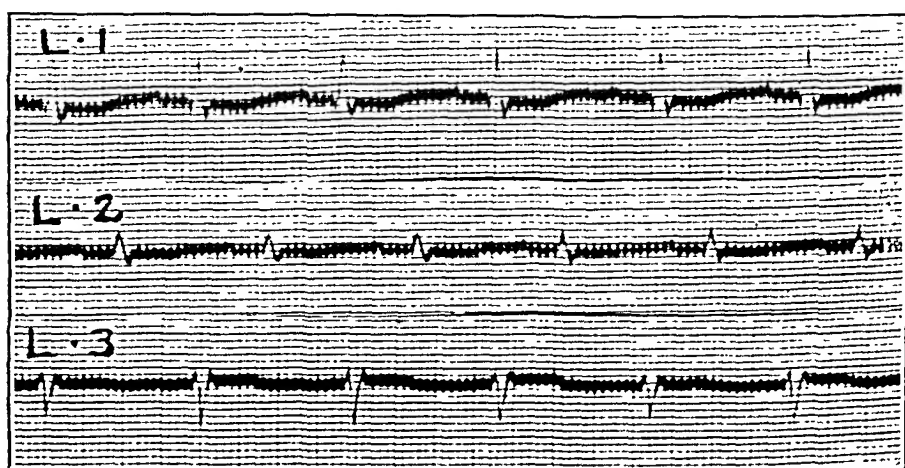


FIG. 6.—Case II. October 15. Quinidin, 2 gm. daily. Normal sinus rhythm.

indicating that in the absence of gross cardiac disease this type of paroxysmal tachycardia does not give a bad outlook.

Of 50 cases with organic heart damage, 40 or four-fifths, were dead within three hours to six months of the onset of the tachycardia, with an average of twenty-four days. Most of these received no specific treatment. Of the 16 cases receiving quinidin only 3 died.

Report of Cases. CASE I.—W. O., a teamster, aged forty-nine years, was admitted June 12 with a complaint of shortness of breath. The past history was negative; venereal infection was denied. A wife and two children were alive and in good health. Nine weeks prior to his admission he had experienced gripping sensations in his chest accompanied by a feeling of suffocation and shortness of breath. From the onset he had about one attack a day, sometimes associated with localized precordial pain, often brought on by exertion. He went to the outpatient department of another institution where he was given intravenous and intramuscular injections following a blood test. Seven weeks from the onset orthopnea appeared, gradually becoming quite severe.

On admission, he was somewhat dyspneic upright in bed. The right pupil was larger than the left and reacted sluggishly to light. The carotids pulsated markedly as did the left subclavian. There was no tracheal tug. The heart was markedly enlarged, 12 cm. to the left in the sixth interspace, with the retromanubrial dullness measuring 8.5 cm. The sounds were of poor quality, regular, rate 100. Systolic and diastolic murmurs could be heard at the apex and a to-and-fro murmur at the base, loudest to the right of the sternum. The radial pulses were regular, synchronous and equal. The blood pressure was 145 systolic and 55 diastolic. The liver edge was palpable 10 cm. below the costal margin. There was no fluid in the abdomen, and slight pitting edema of both legs. The urine was negative and the blood Wassermann positive. The diagnosis of syphilitic heart disease, aortitis and dilatation of the aorta was supported by roentgenologic study.

Tincture of digitalis was given by mouth, 16 cc. the first day and 4 cc. daily thereafter for one week. The patient seemed to be fairly comfortable in bed, with occasional attacks in which there was a sense of suffocation. However, ten days after the discontinuance of digitalis, a suggestive fluid wave appeared in the abdomen, and digitalis was recommenced, 24 cc. of the tincture being administered during the next forty-eight hours. Following this, the pulse developed a rapid slight irregularity characteristic neither of auricular fibrillation or flutter. Electrocardiograms taken at once showed the rare form of ventricular tachycardia with bidirectional alternation of the complexes seen in Fig. 2, and periods during which slow supraventricular beats were interrupted by numerous premature systoles of ventricular origin. Digitalis was omitted and no other medication employed. Two days later the pulse was slow and the patient was free of symptoms referable to the rapid rate. Four days after this sudden death occurred.

Autopsy revealed an adherent pericardium, a normal myocardium and endocardium, and normal coronary arteries. There was typical syphilitic puckering, commencing in the midportion of the ascending arch of the aorta and two thin-walled saccular dilatations, each about 1.5 cm. in diameter were present. The liver and spleen showed passive congestion. Other organs were not remarkable.

CASE II.—G. R., a retired laborer, aged seventy-three years, was admitted September 16, complaining of shortness of breath and precordial pain. The past history was negative for rheumatic and venereal infection. Three

children had died in infancy; the fourth was adult, living in good health. During the ten months preceding admission, he had suffered from shortness of breath upon exertion and edema of the legs; this had become markedly exaggerated in the last two months and orthopnea had appeared. On the morning of admission he had had a very severe attack of sharp, distinctly localized precordial pain.

Examination showed a very seriously ill man, quite orthopneic, cyanosed, with distended, irregularly pulsating veins in the neck, fluid in both pleural cavities, ascites, a liver 4 cm. below the costal margin, and massive edema from the abdominal wall down. The pupils were very slightly irregular and reacted sluggishly to light. The heart was markedly enlarged, the retromanubrial dullness being 8 cm. and the apex in the fifth interspace about 12 cm. to the left of the midsternal line. At the apex a dull systolic murmur replaced the first sound and the second seemed distant. At the base the sounds were slightly clearer, with an accentuation of the second sound to the right of the sternum. The peripheral vessel walls were thickened and the fundal arteries very slightly tortuous. The pulse was totally irregular, with many feeble beats, and a deficit of 20 at the wrist. The apex rate was always above 120. The brachial blood pressure was 160 mm. systolic for the average strong beats which were noted, although many were lower. The blood Wassermann was negative. The urine showed a faint trace of albumin and no formed sediment. A teleroentgenogram confirmed the size of the heart. The diagnosis was arteriosclerotic heart disease, auricular fibrillation, marked decompensation and questionable coronary occlusion.

Digitalis, 1.1 gm., was given on admission and 1.6 gm. during the following four days. Marked improvement occurred in the general condition of the patient, the pulse deficit disappeared and the rate fell to 80. Purine diuretics were employed with moderate diuresis, but considerable edema persisted. A daily dose of 0.1 gm. of digitalis was instituted. On the fifth day of this dosage, Cheyne-Stokes respiration made its first appearance and the pulse rate showed an alternation between a rapid, perfectly regular rate of 140 and a slow, irregular bigeminy. Electrocardiograms taken at this time showed periods of ventricular tachycardia alternating with a slow, irregular coupling, consisting of a supraventricular beat followed by a premature ventricular systole, this phase exactly as in digitalis intoxication (Fig. 3). Digitalis was discontinued.

Clinically, there seemed to be a vague correlation between the Cheyne-Stokes respiration and the rate changes. Simultaneous pneumographic and electrocardiographic tracings indicated no definite relationship between cardiac and respiratory phases except that in general there were as many alternations between tachycardia and coupling as there were between apnea and dyspnea.

Carbon dioxid inhalation was given to the patient later in the day with the production of deep, perfectly regular hyperpnea, but without any effect on the alternation of paroxysms of tachycardia. Adrenalin (1 cc.) given subcutaneously produced no effect upon either the respiration or the pulse. Vagal and ocular pressure likewise proved ineffectual. Since Gold and Otto had reported the almost complete disappearance of digitalis bigeminy under atropin⁵¹ and Reznik and Lathrop had reported a case in which Cheyne-Stokes respiration produced an effect on the cardiac rhythm through the vagus⁵² atropin was administered subcutaneously in dosage of 2.2 mg. No effect on either heart or respiration was produced in forty minutes when the dose was repeated and observations continued. Although well-marked signs of atropin effect were noted in dryness of the mouth and dilatation of the pupils, the electrocardiograms continued to show the same rhythmic changes.

After the paroxysms of ventricular tachycardia had persisted for ten days in spite of withdrawal of digitalis, the general condition of the patient was decidedly worse. Marked venous stasis was evident and edema was even greater than on admission. Quinidin therapy was decided upon and the sulphate administered by mouth. Under dosage of 0.8 gm. per day slow bigeminal rhythm became the dominant mechanism, with rare paroxysms of tachycardia. With a dose of 1.2 gm. daily the rhythm changed to that of slow fibrillation with some premature ventricular systoles (Fig. 4). Increasing the quinidin to 1.6 gm. per day produced the electrocardiogram shown in Fig. 5, suggestive of a very slow auricular fibrillation, and finally with a daily dose of 2 gm. normal sinus rhythm was restored (Fig. 6). In spite of the slower regular rate and the absence of excessive venous stasis the patient failed to show any improvement and sank slowly into a stupor followed by exitus. Permission for autopsy could not be obtained. In this case the relationship of the paroxysms of tachycardia to the digitalis medication seems much more obscure than in the preceding case. Whether the earlier administration of quinidin might not have been of greater value cannot be said, but the ten days of tachycardia had undoubtedly weakened what little cardiac reserve had been present at the onset.

Summary. 1. Sixty-three cases of paroxysmal ventricular tachycardia found in the literature and 2 of the writer's here presented have been analyzed.

2. No common single etiologic factor could be discovered, but 84 per cent of the cases occurred in patients suffering from organic heart disease, and of these 60 per cent had been treated with digitalis prior to the onset of the tachycardia.

3. In the absence of organic heart disease the prognosis of paroxysmal ventricular tachycardia is good.

4. Probable diagnosis may be made at the bedside in seriously ill patients, and quinidin therapy instituted, with uniform success in ending the tachycardia.

NOTE.—I wish to express thanks to Dr. Soma Weiss for his guidance in the preparation of this paper and to Dr. Ralph C. Larrabee for permission to use these cases.

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THE USE OF BACTERIOPHAGE FILTRATES IN THE TREATMENT OF SUPPURATIVE CONDITIONS.

(REPORT OF 300 CASES.)

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AN experience involving approximately 300 cases treated by the local application of bacteriophage filtrates to a wide variety of suppurative lesions permits one to make a number of observations concerning the type of case suitable for such treatment, the best method of application, and the therapeutic results attained, which a smaller series would hardly justify. Many other cases in the care of colleagues have been reported to me but not made the subject of

this report except in a few instances, when they were well-worked out. In the main, our results have been surprisingly good.

Most of the first 50 cases treated received active strains of bacteriophage as determined by tests *in vitro* against the autogenous cultures. In more recent work, we have wished to get the treatment out of the laboratory stage, and have for the most part used polyvalent stock preparations made by mixing various filtrates representing several bacterial cultures (*Staphylococcus* and *Bacillus coli*), and as many homologous bacteriophage strains. The advantage of the stock preparation is obvious in that it is immediately available when needed, is much less expensive, and can be made in large amounts and kept rather indefinitely. Stock preparations have seemed to be just as good as those prepared for a specific case, except that they have not "hit" quite so certainly. When the stock preparation has proved ineffective, we have tested it out against an autogenous culture of the offending organism to determine whether or not it would cause lysis. In nearly every such case we have found that the stock preparation was not active or was very slightly so. If then an active bacteriophage strain from some other source could be found it was used, and if it was effective was then added to the stock preparation for future use. The sources of our bacteriophage strains have been a laboratory strain of great potency (the original Gratia strain) and other strains isolated by ourselves from the pus of spontaneously healing lesions, or from the sewage of the city of Indianapolis.

We shall not attempt to discuss in this paper the problem as to how the filtrate acts in achieving the results obtained, but wish to say that we appreciate the fact that there are other factors than the pure Twort-d'Herelle phenomenon which may be involved. The filtrate which we have used has been a meat extract or meat infusion peptone broth, pH 7.6 to 7.8 when made, in which bacteria have grown for from two to twenty-four hours before being partly or completely lysed by the addition of active bacteriophage, and which has then, after twenty-four hours, been passed through a Seitz or a Berkefeld filter to sterilize and remove material in suspension.

The results which we have seen may have been due to one or more of the following theoretical possibilities:

1. The action of the bacteriophage as a lytic agent capable of destroying the offending organisms in the manner described originally by d'Herelle.¹

2. An antiviral effect such as Besredka² has described.

3. The effect of an extremely available antigen in the form of the dissolved bacterial bodies as suggested by Arnold and Weiss.³

4. The induction of the offending organism into an avirulent phase as a result of the microbial dissociation enforced by the presence of the bacteriophage as pointed out by Hadley.⁴

5. The effect of the stimulation of the tissues by peptone broth as has been worked out by Friedländer and Tooney.⁵

We have in mind merely to report a summary of results in certain groups of cases without attempting to say exactly which of the above possibilities is responsible except to say that the last, that of Friedländer and Tooney, could not have been the *sole* cause of the marked improvement so often observed. We treated several cases with peptone broth and saw some improvement, as might be expected, but never observed striking effects.

Boils and Carbuncles. Sixty-six cases treated, with excellent results in 55, intermediate results in 5, failure in 5, and no report in 1. At least 4 of the failures may probably be explained by the fact that the organism responsible (streptococcus in 2 and resistant staphylococcus in 2) was not susceptible to the bacteriophage strains at our disposal, as was determined by tests *in vitro*. In other cases with relatively unsatisfactory results the lesions were so deep that local application of the filtrate could not reach the site of the actual infection. Permission to inject was not granted.

We have had 10 cases of generalized furunculosis of extreme grade—fifty to three hundred and fifty boils present simultaneously in each case—in children from five months to ten years of age. All of these have shown spectacular improvement immediately after the application of the bacteriophage. Most of these children were in bad condition when we began treatment—emaciated, badly nourished, running considerable temperature, extremely uncomfortable, and in several instances considered to be critically ill. The bacteriophage was applied directly as a wet dressing, or in several instances injected directly into the lesions with a fine needle. In every case except one the child was markedly improved the following day, the temperature was lower, the pain and soreness less, the early boils tending to abort, the older ones moving rapidly toward liquefaction, and the child apparently turned toward recovery.

Several carbuncles have been promptly helped in a striking way. Boils in the nose and external ear canal have usually been less painful and have rapidly come to a head when treated with pledgets of absorbent cotton wet with the filtrate and changed every hour or so. Particularly desirable is the fact that these very painful and even dangerous boils may be treated effectively by this method without manipulation that may cause them to spread. Styne in a few cases has responded nicely. Several of our patients with boils have been diabetics, and have shown good results except that the lesions have possibly been a little slower to close.

Patients with "crops" of boils have usually obtained relief from the effects of the particular lesions, but in only about half of the cases has the attack entirely stopped. Bacteriophage does not always immunize the individual against subsequent boils though it

has sometimes apparently done so. We have in mind perhaps a dozen individuals who have continued to have boils but have controlled them quite easily when they have appeared.

Superficial or opened boils have simply been treated with a wet dressing of the filtrate; deep lesions have been injected, or treated with a wet dressing after having had the skin broken with a needle or scalpel. In some cases we have applied the bacteriophage suspended in a 1 per cent agar jelly. In nearly all cases there has been a marked diminution in the pain and soreness, the necrotic core has liquefied rapidly and has easily come out leaving a clean crater which has healed in the minimum time. Frequently the relief has been surprisingly prompt. Early boils have frequently been aborted. We have not injected bacteriophage into the arm as is advocated by Larkum⁶ and many others; nor have we used the filtrate as one would use a vaccine as recommended by Arnold and Weiss.³

A large number of workers have used *Staphylococcus* bacteriophage in the treatment of boils and related lesions. Bruynoghe and Maisin⁷ seem to have been the first (1921) to report favorable results in furunculosis. Gratia,⁸ the discoverer of the highly potent strain which bears his name, reported soon after (1922) favorable results in a wide variety of staphylococcus conditions. Gougerot and Peyre,⁹ in 1924, got favorable results in staphylococcus lesions. More recently Hauduroy, Camus and Dalsace,¹⁰ Hauduroy,¹¹ Rice,¹² Grenet and Isaac-Georges,¹³ Larkum,⁶ Lingeman¹⁴ and others report favorably.

Abscesses. Twenty-seven cases; 24 are reported as having shown excellent results, 1 intermediate, 1 no improvement, the primary condition having been hopeless and 1 no report. If the abscess had been opened as was usually the case, the phage was simply instilled or injected into the cavity by means that seemed appropriate at the time. We have commonly anchored a catheter in deep lesions and have then injected the filtrate with a glass syringe into the open end of the tube. Recently we have injected the filtrate suspended in a 1 per cent agar jelly when the cavity was in such position as to allow the liquid filtrate easily to leak out. Such an agar preparation readily passes through a syringe and has given particularly good results. The attendant should be warned not to be alarmed by the appearance of the agar as it may come from the abscess cavity.

Many of the abscesses treated were of months' duration, and a few had been draining for years. A sinus and abscess of seven years' duration having not once been closed in that time, healed completely in three weeks and has since remained sound. A large chronic abscess at the site of a nephrectomy operation done several years before was 6 inches deep and had a capacity of more than 100 cc. by accurate determination. The patient's color was bad, he had considerable temperature, was badly emaciated, and otherwise in an unsatisfactory condition. After the injection of bacteriophage into

the cavity he showed prompt improvement, the wound closed completely, and he gained 22 pounds in an interval of five weeks.

Particularly good results were obtained in these cases in which the abscess had not been opened when we first saw the patient. The filtrate was injected through a fine needle directly into the cavity, or into the badly inflamed tissues about it. The injection was repeated until the area became markedly fluctuant, and the soreness and signs of local inflammation had abated. When this state had been reached, the abscess was opened with the smallest incision that would serve the purpose of draining the highly fluid pus. The lesions have then healed with the rapidity of a surgical incision. There may seem to be some objection (as judged by past standards) to the closed treatment of an abscess after it is evident that it contains fluid pus, but there can be no danger when the temperature and the signs of local reaction have abated as has been rather uniformly observed. The closed method has the advantage that secondary infection of the abscess is avoided, the smallest possible amount of bacteriophage need be used, and there is decreased danger of spreading the infection when the well-localized abscess is opened.

Staphylococcus Cellulitis. In addition to the above cases of abscess, may be mentioned five others of *Staphylococcus cellulitis* of marked grade, which were all treated successfully with phage after other means had failed. All of these lesions were large, extremely painful, causing considerable temperature, and stubbornly refusing to localize and liquefy. Three of the patients were considered by clinicians to be critically ill. Bacteriophage was injected in several places into the board-like tissues—usually about 0.5 cc. being used in each place. Needless to say this is a painful procedure, but may be relieved by the use of gas or other short anesthetic. The pain of injection, being due to increased tension, is, at the worst, of but a few minutes' duration, and is followed by marked relief.

The rate at which these lesions came to suppuration, and later to healing, was uniformly surprising. In each instance, the patient rested well the following night after having had little rest for days or even as long as three weeks before. The following day considerable pus was present, but was not released until highly fluid and sharply localized. Studies by Nelson¹⁵ and by Smith¹⁶ have shown that bacteriophage filtrates have great power to promote phagocytosis of the homologous organism. Hadley⁴ points out in his splendid review of the literature on microbic dissociation that bacteriophage in one of the very best means of causing a culture of bacteria to turn "rough" and that when rough the organisms are much less pathogenic, and much more susceptible to phagocytosis. This doubtless explains the rapid suppuration and the prompt liquefaction of the necrotic material in the abscess cavity. We have commonly observed a marked increase in pus production on the day following the application of the phage. This is regarded by us as an omen of great

promise inasmuch as it means that the reagent is active against the particular lesion being treated.

We have often been struck by the vividness of the description of the results of various experimenters, and until we had had personal experience were much inclined to be skeptical of them. We have, however, been able to verify these findings repeatedly. McKinley,¹⁷ Hauduroy^{10,11} and others give glowing accounts of the prompt relief of pain and rapid return of function. To be sure Besredka² describes exactly the same results following the use of his antiviral (filtrates of old staphylococcus cultures). Bazy¹⁸ ascribes the good results to the presence of the soluble products of the lysed bacteria, and doubts if the bacteriophage has much to do with it except to cause the lysis. Arnold and Weiss³ emphasize the importance of the highly available antigen that is produced by the solution of the bacterial substance.

Staphylococcus Purulent Arthritis. Four cases (nine different joints); excellent results in all. The phage was injected directly into the involved joint cavity after pus-containing *Staphylococcus aureus* had been aspirated. In every joint there was improvement, and in nearly every one there was restoration of complete function (observation of Dr. Garceau, resident of Riley Memorial Hospital, Indiana University). One of the children died subsequently of another condition. At autopsy the two shoulder-joints, both of which had been seriously involved, filled with pus and injected with bacteriophage, were found to be in normal condition and had given perfect function for weeks before the death occurred.

Appendiceal Abscess. Seventeen cases; 14 excellent results, 2 good and 1 failure. The failure was a child that was evidently moribund from advanced general peritonitis. Death occurred a few hours after the child was first seen by us. The phage was only put into the opening of the abscess since permission was not granted to inject it into the peritoneal cavity. In all of these cases a mixed *Bacillus coli*-*Staphylococcus* bacteriophage was used. We repeatedly saw rapid healing of the lesion even though the tissues were covered with fecal material from the bowel. One of these cases was described at a county medical meeting as being quite hopeless. Several members of the society agreed that the child would in all probability die in a few days. She was in coma-delirium, temperature high, abscess very foul, and showing much fecal drainage. The day after phage was started she was definitely better for the first time, and continued rapidly to complete recovery.

Peritonitis. Three cases, all desperate, have been treated, not counting the one mentioned just above. Two are now alive and well. The third died of acute heart failure several weeks after the height of the infection. This man seemed well along toward recovery after a desperately stormy course, but was found at autopsy to have several deep abscesses which had not been found and treated *antemortem*. The filtrate (mixed coli-staph) in these cases was

instilled into the laparotomy wounds. It was, of course, impossible to say how far it penetrated or how it acted in relation to the peritoneum. All of these cases received every other good treatment that the staff could devise. We believe that bacteriophage was but one of half a dozen agents which helped in the results. Inasmuch as it was the only *new* factor in the therapy, we feel that it was a distinct and valuable contribution. These patients were extremely ill and it is likely that failure on the part of any one of the remedial measures would have precipitated disaster.

Puerperal Sepsis. Our one case was desperately ill when she was brought to the University Hospital. As a last resort the attending physician suggested injecting bacteriophage (coli-staph) directly into the cavity of the infected uterus through a sterile catheter. The condition of the patient seemed to justify this dangerous procedure. Injection was made several times during the next two days. The temperature fell rapidly beginning a few hours after phage was begun, and the clinical condition improved. Treatment of so unusual character seemed no longer indicated and the injections were discontinued. The patient recovered, but it was impossible to say whether phage was the real cause or may have been used coincidentally with spontaneous improvement.

Fecal Fistulæ. Four cases with infected fecal fistulæ have been treated with cure in 2 and failure in 2. One of the later died of the primary condition before time enough had elapsed for the phage to have had a fair trial. The other was a child in a critical condition from tuberculous peritonitis with fecal fistula and marked secondary infection—usually considered to be a hopeless combination.

One of our recoveries was probably our most striking case. A young woman had a condition diagnosed by many different physicians as tuberculous peritonitis with fecal fistula. The diagnosis was confirmed early in the course by a surgeon with the abdomen open. When first seen by us she had been ill for something over a year, and no one had given her the least hope of recovery. At the time she was running a temperature of 103° to 104° F., was comatose or in delirium all of the time, was extremely emaciated as a result of the infection and the inability to eat or retain food except in very small amounts. All of the bowel contents were coming from the fistula, which was evidently high. She was being given as many as three intravenous dextrose injections daily. About the opening of the fistula there was a deep ulcerated area about 5 inches in diameter, and undermined most of the way around as much as 3 inches. A wide variety of therapeutic agents had been used without success; she had grown progressively worse, and was to be sent home because nothing could be done. At this time we began instilling mixed bacteriophage (coli-staph) into the ulcer and fistula. In a week there was definite improvement as shown by lower temperature, less

odor, and a better general appearance. After several months of practically constant improvement she went home well, weighing 122 pounds (normal weight for one of her height, 119). During the next four months she did washing, ironing, cooking and cleaning for a family of eight, and has now for several months worked fifty-five to sixty hours a week in a laundry. When last seen the lesion was entirely closed, she weighed 142 pounds, and appeared to be in the best of health.

Possibly this was not a case of tuberculous peritonitis though the diagnosis was made at the time of the abdominal operation, was repeatedly confirmed, and never questioned until the patient was nearly well. Bacteriophage, of course, had no effect upon the tuberculosis as such. The effect could only have been that of controlling the secondary infection—a most important matter in tuberculosis. If this was tuberculous peritonitis it was one of the extremely few who get well after the complication of serious secondary infection and fecal fistula has developed.

Urinary Fistulæ. Five cases; 2 excellent results, 2 that were good and 1 that was poor. In all of the cases the characteristic pus discharge was checked and the lesion became clean or relatively so.

In 2 cases the tract became clean but would not close. It is likely that epithelium had grown into the fistulous canal making closure impossible. The nature of the lesions made it difficult to destroy the epithelium.

Cystitis. Three cases gave excellent results. The coli-staphylococcus mixed phage was instilled into the bladder and retained as long as possible. We obtained no such spectacular results as are reported by Frisch,¹⁹ but were well pleased. Another case not treated was of particular interest. A woman had been suffering from a severe cystitis, and a specimen of urine was sent to the laboratory for isolation of the causative organism and the preparation of a specific phage against it. After three days the filtrate was ready, but was never used for the reason that the patient had suddenly improved markedly. Another specimen of urine taken after the improvement was found to contain a strong lytic agent against the organism isolated before. This woman had developed her own bacteriophage before we were able to get the laboratory strain ready for her. This case illustrates the need of a stock preparation.

Due probably to the fact that d'Herelle worked first with a related organism (*Bacillus dysenteriae*) and that *Bacillus coli* itself is very easily lysed by strains that can be picked up nearly anywhere, infections of the bladder and urinary tract by the coli organism have early and frequently attracted the efforts of investigators of the possibility of phage therapy. A number of workers have reported success, or have made interesting observations concerning the spontaneous development of active bacteriophage strains in cases that

were recovering from various infections of the urinary tract. Prominent among these may be mentioned Beckerich and Hauduroy,²⁰ Larkum,²¹ Ravina,²² Zdansky,²³ Caldwell,²⁴ Dalsace,²⁵ Dutton,²⁶ Philibert,²⁷ Winans.²⁸ Cowie²⁹ reports sterilization of the urinary tract when the phage was given subcutaneously, while most of the other investigators have used it by instillation into the urinary tract. Walker³⁰ in a recent article shows that *Bacillus coli* phage is able to protect mice against large doses of *Bacillus coli* injected intraperitoneally.

Infected Wounds. Forty-four cases; 40 excellent results, 3 good, no effect in 1. There was no apparent reason for failure in the 1 case. The wound contained a staphylococcus which was susceptible to our phage, but it is possible that this was but a secondary invader, and that the real etiologic agent was something else. This was true of 2 other cases not counted above. In each of the latter there were multiple lesions not at all helped by the filtrate. One was found to be due to a yeast infection (monilia) and the other to broken down gummata. For obvious reasons, these 2 cases are not regarded as being suitable for phage therapy and were not counted in the 44 cases.

Very commonly the wounds increased in their pus production for the first twenty-four to thirty-six hours after the first application, but after that they were cleaner, and rapidly developed a healthy granulation tissue. Some patients reported that the liquid caused an intense burning sensation lasting for a few minutes. After this period, however, it was quite soothing. Some found it soothing from the first. Both of these responses were found to presage a favorable result. When the patient experienced neither the burning nor the soothing sensation, the result was likely to be slower or not so good.

Probably as a result of the rapid healing usually observed we have in several instances found the scar remaining to be quite soft and pliable.

Bed Sores. Twenty-one cases; excellent results in 15, good in 2, poor in 1, and in 3 the patient died of the primary condition before there had been time enough for a real trial of the phage. The failure was a boy with several large sores on his completely paralyzed legs. The same number of sores on his back did very much better. We are inclined to think that the failure to close was due to the fact that the tissues were unable to regenerate due to the trophic disturbances which were evidently present. The sores have remained clean or nearly so while the phage has been used.

In reporting that 15 cases gave excellent results we do not mean that all were entirely healed. If the lesion became clean, was granulating, and starting to close in a badly debilitated patient, we have considered the result excellent. Phage can only control the infection with *Bacillus coli* and staphylococcus which is always present in

these bed sores. If the patient's vitality is too low to furnish the actual healing, or if the condition which caused the sore in the first place still exists it is unreasonable to expect complete closure.

Among our patients there were 3 with broken backs. The enormous sores so commonly seen in such cases were in an advanced condition, but all became clean and were closing when death occurred. In one there were multiple lesions varying from 1 to 5 inches in diameter. Those under 2 inches were completely healed and there was a wide rim of new skin about the larger ones, when the patient died. A recent patient in his seventh decade has syphilis and arteriosclerosis of such grade that both legs were gangrenous (and later amputated below the knee) because of the failure of circulation. This man had two deep bed sores over the sacrum. Both became clean and closed completely though they were very slow at the end. The peripheral circulation in this man was so poor that a good result could hardly be expected. Another old man, aged sixty-nine years, had a large prostate, residual urine, cystitis, paraurethral abscess, suprapubic cystotomy wound, septic temperature and two bed sores (one was 4 inches in diameter and the other 2 by 4 inches). We were given the case at the same time that his people were notified that he could live but a short time. He made a complete recovery, beginning to show improvement within twenty-four hours after the first application of the filtrate. A year later he came back to have the large prostate removed and the suprapubic opening closed. At this time he was found to be in good physical condition, and the scars where the two bed sores had been could hardly be distinguished from the neighboring skin.

All of our patients with bed sores were, of course, given the very best general treatment available, but no other medication was used on the sores except that in a few instances Balsam of Peru was used after the sore was clean—and if the proliferation of epithelium seemed in need of stimulation. In several instances we saw the wound healing in a satisfactory way while the general condition of the patient was getting worse. In practically every case phage has checked the offensive odor that makes bed sores such a trial to the family and the nursing staff. This is an achievement of considerable value even if nothing else comes of the treatment. One patient dying of tuberculous meningitis had four enormous bed sores. The two worst ones were treated with phage, the other two according to the hospital routine. A week later the man died, and it was found that the two sores treated with phage were decidedly cleaner and healthier in appearance. This is not in accord with the usual theory that phage spreads rapidly to remote parts.

Leg Ulcers. Three cases; 2 excellent results and 1 good result. Two of these cases had been put to bed, and it is not impossible that this is the cause of the good result. In both cases, however, they had already had bed rest, and the patients were sure that the

improvement was more marked after the filtrate was used. As in the case of bed sores, the phage can do no more than help control the infection that is present. Obviously it cannot correct vaso-motor or trophic nerve disturbances. Bizard, Marceau and Rosenthal³¹ report successful treatment of ulcers of the leg with phage.

Perineal Lacerations. Ten cases; results excellent in all. The phage was used as a prophylactic in cases that were handled in the most carefully aseptic manner. The lacerations were repaired in the usual way, and then bacteriophage was allowed to run over the stitches, being applied three times a day as a rule. In all there was rapid healing without pus or evidence of inflammation. Probably all would have done well without phage, but it seemed as if these cases did particularly well (opinion of Dr. Bedwell, resident of Coleman Hospital). Three of the patients had third-degree tears (involving the rectum) and were certainly contaminated. One of these women had a normal bowel movement without aid on the eighth day and went home on the ninth.

Osteomyelitis. Eleven cases; 4 excellent results, 3 fair, and 4 no effect. Our general impression is that in osteomyelitis the value of phage is less than would be indicated by these figures. If there is dead bone in the lesion it has apparently little or no value. When all necrotic bone has been removed, we have obtained good results, but under such circumstances the result may have been good without phage. In this connection it is interesting to note that Albee³² has a theory that the efficacy of the Orr closed treatment for osteomyelitis is merely a means of causing the patient to develop his own bacteriophage. If this view is correct it should be possible to find the active phage in pus from such lesions when the case is removed. We are at present testing this point in a series of cases, but are not ready to report.

Infected Tuberculous Lesions of Bone. Two cases were attempted; both were failures. It was hoped that we might be able to control the secondary infection and in that case the bone might be able to overcome the tuberculous process. Both were treated for several weeks with no evident improvement. It is likely that there was dead bone in each.

Mastoidectomy Wounds and Running Ears. Nine cases; 6 excellent results, 2 good and 1 failure. If there is dead bone in the mastoid region, failure may be expected. Several of these cases had been running for years, and were dry and odorless for the first time in months within a week or ten days after phage was used. We were not able to ascertain whether the condition returned at a later date in these cases.

Sinusitis. It is almost impossible to estimate the results in these cases inasmuch, as we mostly had to depend upon the patient's description of his feelings. In several instances we have felt that our friends were trying to please us by reporting that they thought

they were "some better." Since the tendency of an acute attack is to improve, it is likely that some of our "cures" were spontaneous. Furthermore, a considerable number of our cases treated for this condition have not returned to report or to continue treatment. A few have had surgical conditions in the nose that would make any sort of medical treatment futile.

We have, however, had some results that were decidedly gratifying, and are responsible for our intention to continue the work further. A prominent physician who has had serious sinus trouble for years reports that he is much pleased with results in his own case, and is emphatic in his insistence that we continue. Inasmuch as he has had a static condition for a long time and is well informed on the subject, we are inclined to give ear to his opinion. A few cases have had Roentgen ray examinations before and after, which seem to show improvement. Two very bad cases have been able to remain during the winter in our irritating climate, while heretofore they had found it necessary to go to the southwest during that season. In all we have had 15 cases that have given the phage a fair trial. In 7 we have thought the results excellent; in 4 good; and in 4 there have been failure. If every case seen were reported, the number of failures would be greater, but we have only counted such cases as continued the treatment long enough to make it reasonable to expect something.

The difficulties are several in this work. In the first place, it is hard to know with certainty that one has the right organism; the filtrate is hard to apply; and finally it is sometimes impossible to evaluate the results with accuracy. Most of the cases have been treated with phage developed from autogenous cultures. Several patients have found the filtrate quite irritating, but this is not unlikely, partly or entirely, due to a lack of isotonicity—a point to be corrected in the future. We have a rumor that a patient using a stock preparation, not under our supervision, had an allergic reaction of acute nature after dropping the filtrate into his nose.

There is much to be done in connection with the use of bacteriophage in the treatment of sinus infections, but we have seen results sufficient to encourage us to go ahead with it. Schumm and Cook³³ report negative results in the main, but there is some reason to criticize their methods. Hayes³⁴ reports that he has had good results with the use of Besredka's antiviral in sinus infections. He used it in essentially the same way that we have used our filtrates. It is not impossible that our results have been due to the antiviral action, or it may be that Hayes had a spontaneously developed phage in his old broth cultures. It is unnecessary to remind the reader that a reagent that would really cure even a small percentage of chronic sinuses would be a great success.

Staphylococcus Septicemia. Two cases. In each case the patient died, as was to have been expected after the blood had been

found repeatedly positive for staphylococcus. One of the cases was moribund when we began, the other lived for weeks longer than was expected, and it was thought that this may have been due to the effect of the phage. The filtrate was not injected intravenously in either case as we were afraid of the effects of the peptone broth. Open lesions in the cases were treated and subcutaneous injections were made. Dutton³⁵ reports that he has seen several recoveries believed due to phage.

Impetigo. Three cases treated and all did well. One bad case served as a control. One side was treated with phage and the other with ammoniated mercury ointment. Both sides were kept clean in the same manner. The phage side did considerably better.

There are those who believe that the initial etiologic agent in impetigo is a streptococcus, but even so staphylococcus is practically always found as a secondary invader. Staphylococcus phage was used in all of our cases.

Acne. Thirty-five cases; 13 excellent results, 8 fair, 7 no effect, 7 did not return. In the main we have had excellent results in the severe cases with much pus in the skin; fair results in the moderate cases; and no good effect in mild cases. Unfortunately for our purpose it seems that every one who cares enough to come to us for treatment, seems to think his or her case is one of unusual severity. We now refuse treatment in any but markedly pustular cases. Several young people with badly involved faces are now entirely free except possibly for the scars. The pimples become less sore and red, and the face less indurated. In half a dozen cases we have been able to get large amounts of pus from a face that two or three days before was indurated, red and sore. In such instances there was prompt relief. Commonly we have found the skin of our acne cases to be very oily, and after the inflammation has been relieved have recommended Roentgen ray treatments for the condition in the hope that this would prevent recurrence.

In treating acne we have had the patient wash the face with hot water and rather strong soap twice a day. He has then been instructed to open pustules and press out the contents, later wiping the face thoroughly with an alcohol sponge. When the face was dry the phage (*Staphylococcus aureus* and *albus*) suspended in a 1 per cent agar jelly was rubbed into the skin and allowed to remain. It soon disappeared leaving nothing to indicate its presence. Treatment for acne has by no means been a complete success, but we are reminded that no other treatment is such by a very great deal. Most of our cases had "tried everything" before we saw them. A medical student with 30 to 40 ugly pustules all of the time showed prompt improvement, and was entirely well in about a month. He now has an unusually clear skin. No attempt to find a phage active against *Bacillus acne* has been made inasmuch as we have believed that it was of no real consequence in the causation of the condition.

Streptococcus Infections. No attempt has been made by us, as yet, to develop a Streptococcus phage, but in 5 or 6 cases we have begun treatment under the impression that we were dealing with a staphylococcus and have had a good result, later to find that streptococcus was at fault. In at least three of these the phage used was found to be active against the organism. In all the streptococcus was nonhemolytic, and the lesion well localized. In 2 cases of acute streptococcus boils, the Staphylococcus bacteriophage was of no avail. Some of our strains of bacteriophage have been found to be active against certain cultures of streptococcus and pneumococcus *in vitro*. Other investigators have reported good results from the use of Staphylococcus bacteriophage in streptococcus infections as may be mentioned, Dutton³⁵ and Hadley⁴ who refers to the opinion of Larkum and of Pryor. Dutton³⁶ reports good results with the use of what may be a Streptococcus bacteriophage but is not typical. The great number of strains of streptococcus makes the problem one of particular difficulty.

General Discussion. In our opinion bacteriophage therapy is a distinct and valuable contribution to the armamentarium of the physician and surgeon for the treatment of suppurative lesions. It is not a cure-all by any means and the note of warning sounded by the editorial³⁷ in the *Journal of the American Medical Association* is well taken.

In suitable types of infections it may be expected to do certain things which in our opinion cannot be so well done by any other known remedy. Experience is necessary, of course, in applying it so as to get the best results without waste; in knowing when to apply it; and in evaluating the results. Particularly is it important that the physician and the patient be warned that the first twenty-four to thirty-six hours may show a distinct increase in the amount of pus. This is a good sign. Dosage does not seem to be important except that enough must be used to give good contact with the reagent. As a rule we have used larger amounts than the practising physician would feel justified in using because of the expense. Frequent administrations or dressings with it have seemed to give the best results.

We have been anxious to make the preparation available to the profession, knowing that it could be of little use if it must be prepared for each case separately. Most of the last 250 cases have been treated with a stock preparation, the greater part of which has been made under our direction by the Swan-Myers Company of Indianapolis. This company has furnished, without charge, large amounts of the various preparations for the purpose of making a clinical test under conditions as nearly as possible like those in actual practice. The stock preparations have seemed to be just as good, except in a very few instances, as the phage prepared by the laboratory for a particular patient.

In the beginning of our clinical work we would accept for treatment only those cases that were considered by the staff or the physician-in-charge to be in a hopeless condition, and on which permission was granted to stop all other therapy. There are at present 30 or 40 of these people alive and well. A considerable number of our patients are dead of their original condition though the lesion treated with phage was well at the time of death. A rather large percentage of our cases which turned out favorably were complicated by diabetes mellitus, syphilis, malnutrition, old age, inanition, arteriosclerosis, trophic nerve disturbances or other processes well known to retard healing.

With the exception of the report of the allergic distress following instillation of the phage into the nose, the burning sensation which lasts for but a few minutes in some cases when put on raw wounds, and two or three moderate chills within a few hours of the application, we have seen or heard of no bad results. A number of investigators have been afraid that there might be developed in the patient a strain of phage-resistant organisms which would be more pathogenic than the original. We have seen absolutely no evidence of such a phenomenon, and feel that when phage is applied locally there is no danger of such a result.

Conclusions. 1. In about 90 per cent of cases we have had excellent results with the local application of bacteriophage filtrates (*Bacillus coli*, and various strain of *Staphylococcus aureus* and *albus*) to suppurative lesions due to the homologous organisms.

2. Our experience does not inform us as to the manner in which the reagent acts except that we see evidence of increased phagocytosis and liquefaction.

3. Stock preparations are apparently as good as those specially prepared except in a few cases. Stock preparations have the great advantage in that they are readily available at the time needed, and can be used at a distance from a bacteriophage laboratory.

4. We have seen little or no evidence that the treatment of one lesion or the injection of the phage into an uninfamed area will influence a distant lesion except when there is actual contact with the reagent. We have, however, made very little attempt to study this relation.

5. Dosage does not seem to be important, provided the filtrate is used in sufficient amount to give good contact as a wet dressing.

6. No bad results of importance have been observed. There has been no clinical evidence of the development of resistant strains that were more pathogenic than the original.

7. Bacteriophage therapy should be regarded as an addition to the armamentarium of the physician rather than as a substitute for something already used.

8. Strong antiseptics have seemed to be contraindicated while

phage was being used, but we have no experience to tell us that they would have altered the results.

NOTE.—We must take this opportunity to express our thanks to the large number of clinicians who have coöperated with us and have made this work possible. Particularly have we to thank the staff of the Indiana University Hospitals for their interest and advice.

Readers interested in general discussions of bacteriophagy, and in complete bibliographies are referred to works by d'Herelle,¹ and Hadley.⁴

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THREE METHODS OF OBTAINING INTESTINAL MATERIAL DIRECTLY FOR BACTERIOLOGIC EXAMINATION WITHOUT THE POSSIBILITY OF CONTAMINATION FROM SURROUNDING SOURCES.

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IN the investigation of certain phases of the bacterial flora of the human intestine in living subjects in health and in disease, we were impressed early by the difficulties encountered in securing contents, secretion or excretion from a definite source or location within, and directly from, the intestinal tract without contamination from continuous and contiguous areas. The anatomy of the intestine and our present nonoperative methods of exposure of the part desired for the obtaining of material are such that we do not believe that the probability of contamination from near and adjacent sources has been overcome by present methods.

In recent years the use of the proctoscope and sigmoidoscope has been extended from inspection and treatment of gross bowel lesions to their use in protozoal¹ and bacteriologic investigations of the distal colon² because of the advantages of employing fresh material from direct sources. In the application of this method, as well as in the securing of intestinal material through fistulous openings, sterile cotton swabs on long wooden applicators are usually employed. The difficulties encountered in their use in an attempt to secure uncontaminated material for bacteriologic examination are as follows:

The size of the lumen of the distal intestine afforded by the introduction of a proctoscope or sigmoidoscope is limited. This makes it more often impossible to introduce and withdraw through the instrument without contamination from near and adjacent areas, an applicator of the type usually employed and mentioned above. Also, and again because of the relative smallness of the lumen, one often unavoidably touches with the applicator the distal portion of the proctoscope or sigmoidoscope which frequently contains, even in the presence of an apparently grossly clean intestine, some content or secretion as a result of insertion, advancement and manipulation of the instrument in the intestine.

In order to obviate these dangers of contamination, inherent in both the near and adjacent tissue of a restricted intestinal segment, as well as in the distal portion of the proctoscope or sigmoidoscope,

the following devices have been developed. These may be used separately or jointly depending on both the wishes of the worker and the case at hand. They enable one to secure a sufficient quantity of intestinal material for bacteriologic study which we think can be regarded as representing the true material from the source desired uncontaminated by material from surrounding areas.

1. The first device consists of 7 to 8 mm. soft laboratory glass tubing in three lengths: 8 cm., 17 cm. and 30 cm. Permitting free motion within the glass tube is a cotton swab attached distally to the roughened end of a firm iron wire applicator of 16 gauge. The iron wire applicator is about 12 cm. longer than the length of the glass tubing which encloses it. The increase in length of the iron wire over that of the tubing is the length of that part of the applicator which extends proximally beyond the tubing. This extension is used for two purposes: (1) to make a small handle (Fig. 1), and (2) to permit projection of the applicator for about 8 cm. beyond the distal portion of the glass tube when the device is in use (Fig. 3).



FIG. 1



FIG. 2

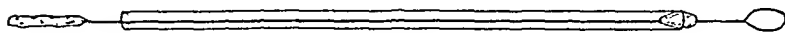


FIG. 3

FIG. 1.—Shows one size of the type device used in the first and third methods completely assembled. After use, the device would appear as in Fig. 3 but without the distal cotton pledget.

FIG. 2.—Shows the device wrapped prior and subsequent to sterilization.

FIG. 3.—Shows the device in use: the projection of the swab beyond the glass tube which protects it from coming into contact with the proctoscope or sigmoidoscope, and from surrounding tissue and sources.

In further preparation, a small pledget of raw cotton is placed at each of the two ends of the glass tube so as to keep the applicator from slipping out at the distal end and to fix it to the tube at the proximal end. The device now being completely assembled (Fig. 1), next is wrapped in paper save for the handle which projects beyond it (Fig. 2). It is sterilized, then, in the autoclave. These tubes may be prepared in quantity in the several sizes and used as desired.

With the proctoscope or sigmoidoscope in place, and if necessary held there with the aid of an assistant, the paper covering now is removed from the sterilized device. Next the distal cotton pledget is withdrawn, the distal end of the device is passed quickly through a flame, and then the device is inserted through the instrument *under the direct vision* of the worker to a point directly over, but not touching the area from which the material is desired. Still

under the vision of the worker, the applicator is pushed forward and the swab now is in contact with the sought for involvement; then, with the glass tube in its original position with relation to the involvement and instrument, the applicator is drawn back into it and only then is the entire device withdrawn from the proctoscope or sigmoidoscope. Care should be taken that the distal portion of the glass container should touch neither the intestine nor any of the contents. As soon as possible thereafter, and immediately subsequent to the flaming of the proximal end of the device, the material-containing swab is removed through the proximal portion of the glass tube so as not to touch the distal end again. The swab is placed now either in a sterile test tube, or the appropriate media are directly inoculated.

By means of this glass tube which encloses the iron wire applicator and cotton swab, the working area through the instrument and within the bowel is much reduced, thus protecting the swab from coming into contact with any of the region surrounding the point from which material is secured, and also from being contaminated by contact with any part of the proctoscope or sigmoidoscope. The 17-cm. long tube is employed when the proctoscope is used; the 30-cm. long tubing, when the sigmoidoscope is used. The 8-cm. length, for securing material directly from the intestine through a fistula, will be discussed later.

2. The second procedure is one which permits the obtaining of contents, secretion or excretion for bacteriologic study, directly from the lower sigmoid through a sigmoidoscope, without contamination either by rectal contents or from other sources. It is a modification of the method described by Andrews and myself for the detection of protozoa from sigmoid contents.¹ The method is as follows:

The patient is placed in Haynes' position, that is, the lower extremities remain on the table, while the trunk, flexed at the hips, is virtually at right angles to the lower extremities; the head rests on the forearms, which are flexed at the elbows and are supported by a footstool of convenient height. This position has been found preferable to the usual, well-known, knee-chest posture. In the Haynes' position the viscera are, by force of gravity, moved out of the pelvis, up toward and against the diaphragm. This reduces intrapelvic pressure and facilitates both instrumentation and the proper execution of this method.

Next, the anus is cleansed, first with green soap and water, then with alcohol if desired, and finally with a 1 to 1000 solution of bi-chlorid of mercury. The right hand is now covered with a sterile glove, the first finger of which is inserted into the rectum so as to stretch the anal sphincter to render more easy the inserting of the sigmoidoscope, if for no other purpose. The sterile sigmoidoscope, covered with a sterile lubricant, next is inserted. The patient is

ordered to take neither purge nor enema prior to this examination, because we learned that any method which results in the thorough cleansing of the rectum will also result in a clean sigmoid with no gross material available for study at either point. If this is done, he usually appears with feces in the rectum. In order to pass from the rectum into the sigmoid so as to secure material from the latter point without contamination from the former source, the subsequent steps are pursued:

With the instrument in the rectum near the feces encountered, the rectal content, diluted when necessary with sterile saline introduced into the sigmoidoscope through a sterile funnel placed in its proximal end, is drawn out through a sterile aspirator 35 cm. by 8 mm., by means of a suction apparatus. In this way the rectal feces is removed without affecting the material in the sigmoid. When the sigmoid is entered, the type applicator described above may be employed to secure through the sigmoidoscope the material desired without contamination from surrounding sources.

Distally lighted instruments are to be used in the execution of methods 1 and 2. The proctoscope and sigmoidoscope used by us, each present a diameter of 16 mm., a diameter no greater than that of the average adult male index finger. An instrument, the diameter of which is as low as 12 to 13 mm., can be used in this work when necessary; however, the former size is to be preferred.

3. The securing of material for bacteriologic study directly from the intestine through a fistula is accomplished by using the iron wire applicator enclosed in a glass tube 8 cms. long. In this case, the paper wrapper having been removed, the sterilized device is inserted, not necessarily completely, directly into the fistula. Excepting that the subsequent steps cannot be performed in their entirety under the direct vision of the worker, they are, however, identical with those described for Method 1. The use of this type applicator in an intestinal fistula presents the advantage of not only preventing the swab from touching the protruding mucosa or adjacent skin, but also keeps the swab from coming into contact with the mucosa of the intestine beyond the fistulous opening upon entry and withdrawal. The contraindications to the use of this device are a fistulous opening too small to permit its entry into the intestinal lumen, and many appendicostomies in which both the opening and appendiceal lumen are too small.

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INTESTINAL PERMEABILITY IN OBSTRUCTION OF THE COLON: AN EXPERIMENTAL STUDY.*

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SURGICAL experience has taught the wisdom of avoiding undue operative manipulation of the distended colon proximal to an obstructed area. It is said that mere handling of the obstructed bowel may cause peritonitis because of the greater permeability of the distended intestine. Our investigation was made to determine whether or not such increased permeability could be demonstrated experimentally.

Early investigations of the permeability of the wall of the bowel for bacteria were concerned mostly with cultures taken from the peritoneal surface, and the blood, after obstruction had been produced. Helmberger and Martina⁴ reviewed the literature up to 1904. The results of cultures in cases of strangulated hernia and in animal experimentation were very contradictory. On the basis of their own observations on rabbits they concluded that the obstructed bowel is permeable for bacteria only in the presence of definite necrosis, and that the muscular layers offer more resistance to bacteria than the other layers. Garnier and Simon³ also found that positive results from culture of the blood in intestinal obstruction depended on the presence of ulceration. In summarizing the literature up to 1923, Rost⁸ said that in experiments to determine the penetration of the intact intestinal wall by bacteria the organisms had been demonstrated only occasionally, and that it was necessary to injure the intestinal wall rather severely before positive results could be obtained from cultures made from the peritoneal surface. Clinical and necropsy observations, however, have been reported of peritonitis which probably arose through penetration of diseased intestinal mucosa, such as occurs in severe enteritis. Aside from the question of bacterial penetration Brooks and his associates² have presented evidence to show that even the toxic element in the content of an obstructed loop is not absorbed unless some circulatory interference has injured the mucosa. Stone and Firor⁹ reported experiments in which they concluded that the raised intrainestinal pressure in obstruction is the cause of abnormal absorption. They injected India ink into the normal small intestine, into the intestine

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partially obstructed by a ligature, and into a loop completely occluded by a ligature at either end. Absorption did not take place under the first two conditions, but in the dogs with completely occluded loops the mesenteric lymph nodes were found to be black. These dogs, however, recovered because the ligature cut through. The injury, incident to this, rather than increased pressure during temporary complete obstruction might well be the cause of the abnormal penetration of the wall of the bowel. That intrainestinal pressure is definitely increased in obstruction has recently been shown experimentally by Owings, McIntosh, Stone and Weinberg.⁷ Kagan⁵ reviewed the literature on the absorption of dyes, such as trypan blue and lithium carmine, and performed experiments on mice. The general conclusion also appeared to be that absorption of such dyes was conditioned by injury to the mucosa. The most recently published review of the passage of bacteria through the wall of the intestine is that of Arnold.¹ He emphasized the significance of the nature of the diet and the reaction of the intestinal content.

In spite of contradictory results, one is impressed by the frequency with which the significance of injury to the mucosa is stressed by various investigators. Most of the foregoing investigations deal with absorption in the small intestine. Since our interest in the subject was aroused by the clinical problem of obstructing carcinoma of the colon, our experiments were restricted to the colon. Because of the difficulty of satisfactorily demonstrating the presence of bacterial cells in the tissues, we chose to use a fine suspension of graphite commercially known as "hydrokollag 300." If penetration of the mucosa and permeation of the wall of the bowel occur in obstruction, it should be readily possible to demonstrate the presence of these graphite particles locally and in remote organs; whereas the search for bacterial cells in stained sections is notoriously laborious and unsatisfactory. Previous attempts to solve the problem by bacterial cultures have not led to unequivocal results, as we have indicated. Soluble dyes might well have a different mode of absorption than bacterial cells. Insoluble particulate graphite, therefore, seemed to us the most suitable substance to employ for this study.

Method of Study. Nine dogs were used. Under ether anesthesia the colon was obstructed by means of a tape ligature about 15 cm. from the anus, care being taken not to crush the wall of the bowel by tying too tightly. Beginning on the day following operation approximately 50 cc. of the preparation of graphite was given by stomach tube on alternate days. The dogs were allowed their usual diet, but most of them failed to eat, vomited and gradually became emaciated and weak. Several recovered and were in good condition when killed. In these, there was practically no obstruction because of the fact that the ligature had cut through. One died sixteen days following operation apparently because of the obstruction. The other dogs were killed at intervals varying from five days to

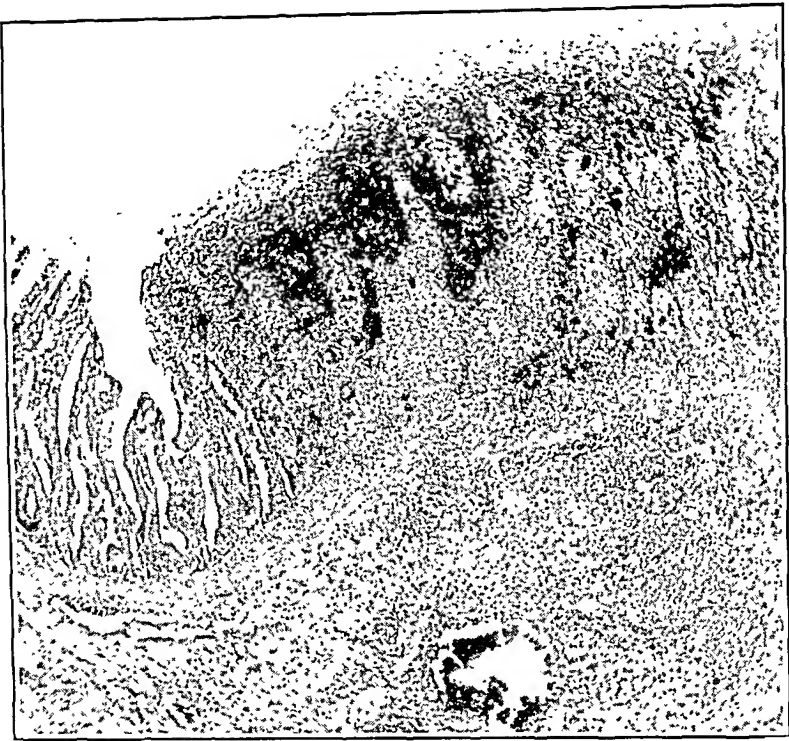


FIG. 1.—Section through a marked hemorrhagic area in the mucosa of the colon of a dog following obstruction ($\times 75$).

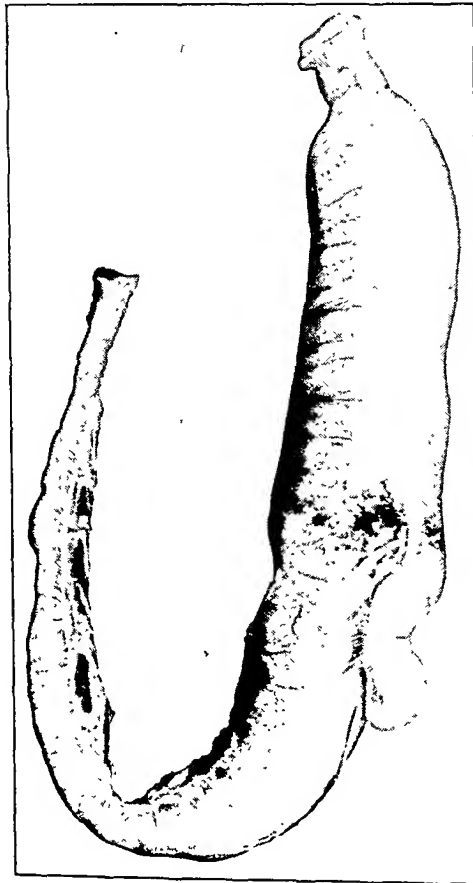


FIG. 2.—The distended colon of a dog, twenty-six days following experimental obstruction. Distention involves a portion of the ileum as well. The black areas should appear red. They are due to hemorrhage, not to graphite.

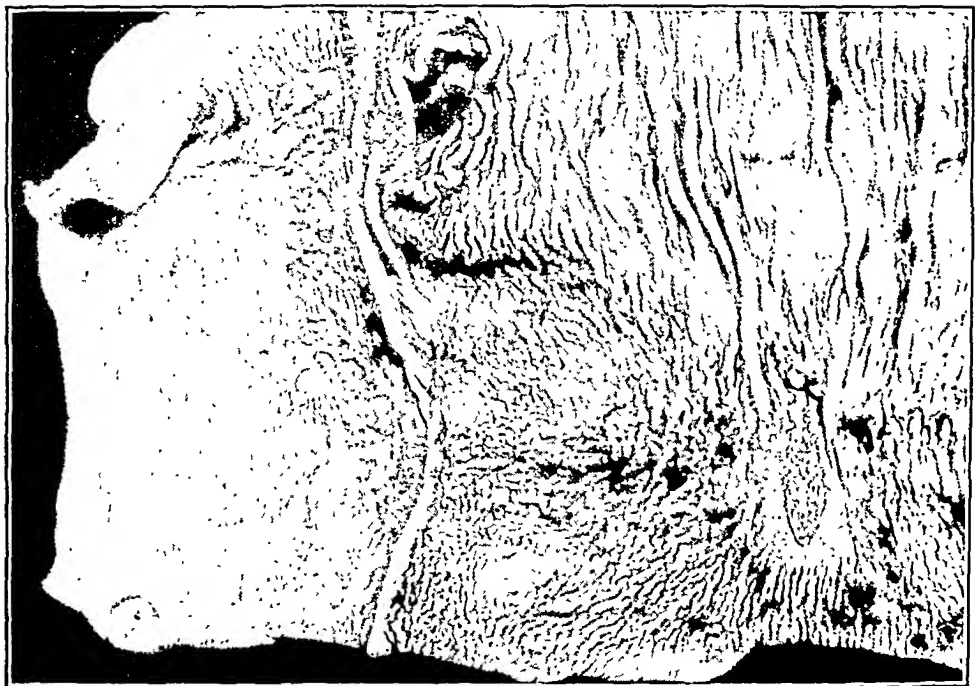


FIG. 3.—The surface of the mucosa of an obstructed colon of a dog, showing ulceration and multiple lesions. Marked pigmentation over the surface is visible. Note ulcerations of the ileal mucosa along the ileocecal valve.

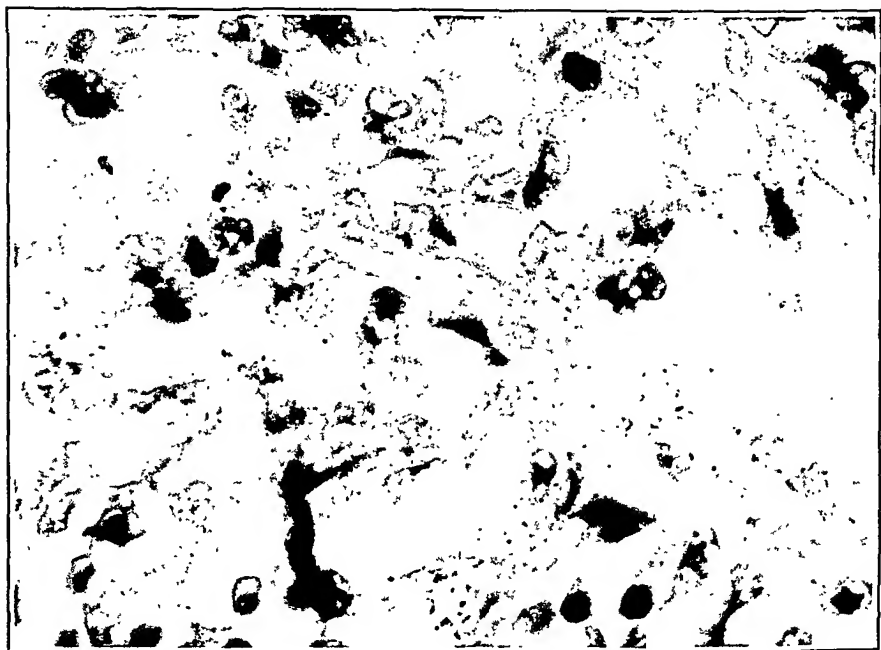


FIG. 4.—Section through the granulation tissue of an ulcer of the colon following experimental obstruction. Particulate graphite is diffusely scattered throughout ($\times 1100$).



FIG. 5.—Section through the liver of a dog whose colon was obstructed and ulcerated. Low-power view, showing diffuse distribution of graphite ($\times 75$).

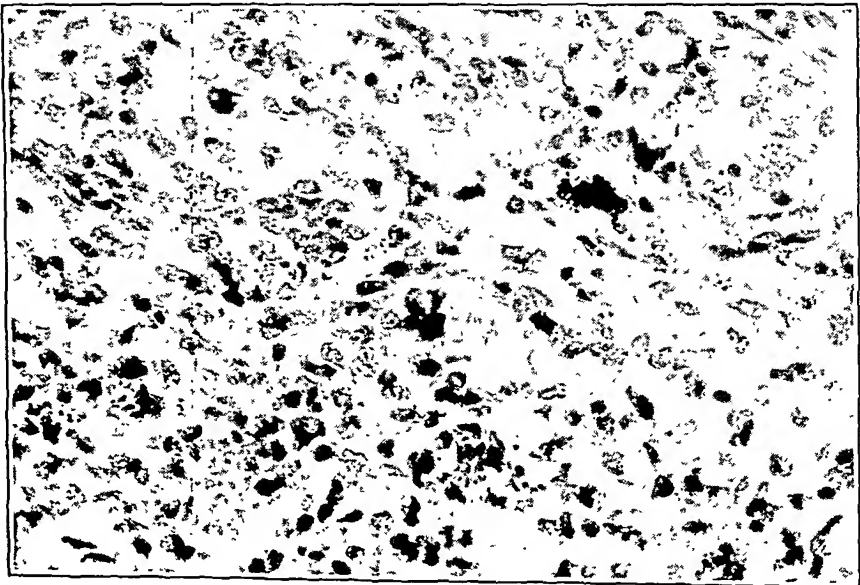


FIG. 6.—Section through the spleen of a dog with obstructed colon with ulceration. Graphite may be observed in blood capillaries and in splenocytes ($\times 450$).

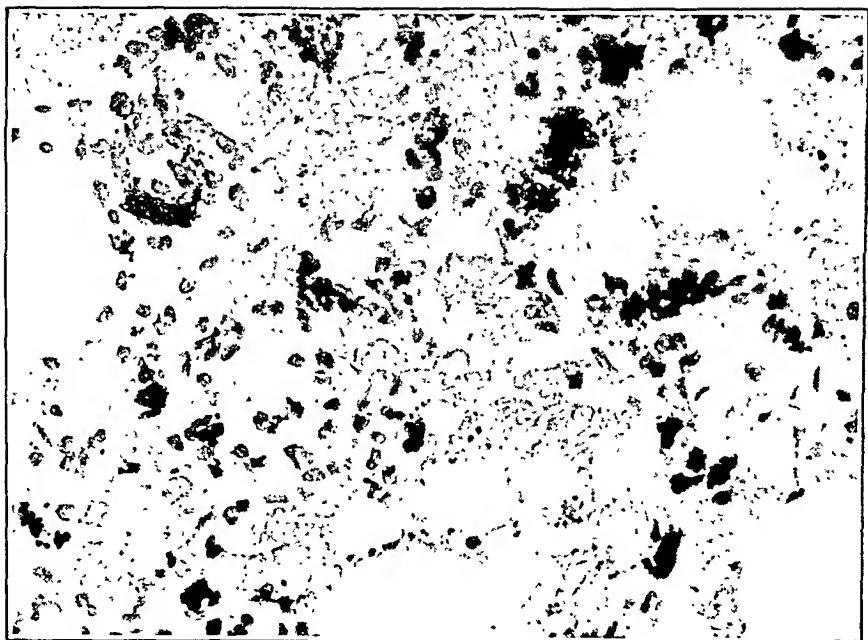


FIG. 7.—Section through the parenchyma of the lung of dog in Fig. 6. Free particulate graphite and large masses in phagocytic cells of the lung may be seen ($\times 450$).

three weeks. The organs were carefully examined for gross evidence of the graphite in the tissues and sections of the colon, small intestine, mesenteric lymph nodes, liver, spleen, lung and heart muscle were taken for microscopic study. These tissues were fixed in formaldehyde and stained with hematoxylin and eosin.

Results. In 6 dogs of our series the search for graphite in the tissues proved entirely negative. One of these was the dog which died. Cause for death, other than obstruction, could not be determined. The colon was markedly distended and was filled with graphite. Ulceration of the mucosa was not found, and particles of carbon did not appear anywhere in any of the tissue. In 2 of the 6 dogs there was practically no obstruction at necropsy two weeks after operation, because the ligature had cut through. Lesions were not found except the healed scar at the site of the ligature, and particles of graphite did not appear in the tissues. In the remaining 3 dogs there was obstruction; in one there was healed shallow ulceration of the colon with lymphocytic infiltration in the submucosa, but in none could the graphite be detected outside of the lumen of the bowel. In 3 dogs there was positive evidence of absorption of the particulate graphite from the obstructed bowel. The necropsy data of these were as follows:

One of the dogs was killed five days after operation because it appeared to be in poor physical condition on account of distemper. Gross evidence of graphite either in the mesenteric lymph nodes or in the subperitoneal regions was not present. The colon proximal to the ligature was distended to about five times the normal size and appeared dark blue, because of the graphite within it. After the colon was opened and washed, the mucosa appeared relatively clear. Several hemorrhagic areas were found on microscopic examination to involve the mucosa and in some regions the muscularis mucosa as well (Fig. 1). Within these hemorrhagic areas were numerous particles of graphite both free and contained in large wandering macrophages. However, particles could not be found in the deeper tissues nor in the intact mucosa. In the liver, on the other hand, scattered black particles appeared in the portal vessels, the sinusoidal spaces, and the central veins. Occasionally such particles could be seen in the Kupffer cells lining the sinusoids. Examination of sections of other organs was negative except for the bronchopneumonic changes of distemper.

The second dog of the series was killed twenty-six days after operation. The animal had continued to lose weight following operation. The entire colon proximal to the ligature was markedly distended. The mucosa of this distended portion as well as two feet of terminal ileum was stained black. This color could be washed from the mucosa with considerable difficulty. Microscopically, it was evident, however, that the staining was due to particles of graphite enmeshed in the surface mucus without penetration of

the mucosa. A shallow irregular mucosal ulcer had developed in the dilated portion of the colon near the point of obstruction; but in this area the particles of graphite were also confined to the mucous deposits on the surface of the mucosa. The stomach contained three superficial ulcers. All the mesenteric lymph nodes were markedly enlarged, but they did not contain particulate graphite. In the liver scattered black particles could be found in the portal vessels and central veins, but they were far from numerous. Examination of all microscopic sections of other organs was negative.

In the third dog, killed twenty-seven days after operation, the entire colon, proximal to the ligature, and the terminal 6 inches of the ileum were tremendously distended, although the obstruction was incomplete (Fig. 2). There were multiple hemorrhagic ulcers in the duodenum, and in the colon there were several shallow irregular ulcerations of the mucosa surrounded by fibrin deposits. A ring of these ulcers was found just proximal to the ileocecal valve (Fig. 3). The under surface of the liver presented a black discoloration suggesting the presence of the graphite, but there were no other gross evidences of absorbed material in any other organ. The mesenteric nodes were not stained, and the thoracic duct, exposed in the chest, was found to be translucent. Microscopically, sections through the ulcerations of the ileocecal area and colon showed granulation tissue with polymorphonuclear and plasma-cell infiltration. Particulate graphite, however, was enmeshed in the surface of the granulation tissue; but none could be identified in the deeper tissues (Fig. 4). Sections of the liver, on the other hand, showed marked evidence of the graphite. Numerous particles appeared, not only in the portal vessels and sinusoidal spaces, but in many of the Kupffer cells which were loaded with the particles (Fig. 5); the same was true in the spleen (Fig. 6). Black particles were abundant in blood spaces, reticulum cells and macrophages. In the lung such particles similarly occurred within pulmonary phagocytes and in the parenchyma as well. These might be difficult to distinguish from the carbon particles of anthracosis; but they did not show a characteristic distribution around the bronchioles (Fig. 7). Results of the examination of sections of lymph nodes, heart muscle and kidneys were negative.

Comment. When this investigation was undertaken it was believed that the tissues of the wall of such an obstructed colon would become thoroughly permeated with the particles of graphite. Such abnormal permeability would offer an explanation for the incidence of peritonitis resulting from handling the bowel and lightly injuring the serosa during operative procedure. Under the conditions of our experiments, however, no such penetration occurred. The only way in which abnormal permeability could be demonstrated in these experiments was not as a diffuse permeation

of the wall of the bowel, but rather as a definite penetration of graphite into the blood vessels of the mucosa and subsequent distribution by the portal blood stream. The only conditions under which such vascular penetration occurs are obstruction, with injury to the mucosa. It appears as if the distending pressure in obstruction actually forces the particles of graphite into the blood stream, but only in the presence of ulceration. Ulceration of the mucosa, without the added factor of marked obstruction, does not lead to this result. There must be obstructive pressure. These observations do not detract from the value of the clinical experience mentioned. It is highly possible, or indeed probable, that in the presence of an obstructing infected ulcer, malignant or otherwise, virulent bacteria actually do penetrate through to the serosa. In the light of our experiments, however; it seems that such penetration must be due to the invasive property of the living bacterial cell, and not to any abnormally increased permeability. Even in obstruction the intact mucosa offers a very effective barrier.

One might speculate on the possible analogy which suggests itself between the results of these experiments and the mechanism of metastasis to the liver. It is an accepted fact that the prognosis in resection for carcinoma of the right side of the colon is better than for a similar condition in the sigmoid, although the growths in the right side are discovered relatively late and are often much larger at the time of operation. The difference is that obstruction occurs earlier on the left side. It is conceivable that in the presence of obstruction and ulceration, cancer cells might be pushed into the portal circulation in a manner similar to our graphite particles. Metastasis to the liver, therefore, would occur relatively earlier and more frequently when the lesion is in the left side of the colon. This mechanism is, of course, only one of many factors to be considered.

Conclusions. The general permeability of the wall of the colon to particulate graphite is not increased in obstruction under the condition of the experiments here reported. In the presence of injury to the mucosa and obstruction, however, particulate graphite may enter directly into the circulation and may be distributed by the portal blood stream.

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INTESTINAL POLYPOSIS WITH AN INSTANCE OF MULTIPLE FIBROMATOUS POLYPS.

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BENIGN tumors of the intestine may be classified according to their histologic structure. Since the wall of the intestine is composed of different tissues, such as glandular elements, areolar connective tissue, muscle, nerve and bloodvessels, benign tumors may be adenomata, including papillomata, fibromata, myomata, lipomata, angiomas and carcinoids, depending upon the site of origin. Dewis¹ in summarizing 219 collected cases of benign tumors of the intestine, found about 60 per cent to be adenomata, 20 per cent lipomata, 18 per cent myomata and 2 per cent fibromata and hemangiomas.

The term intestinal polyp is used morphologically in a general sense to mean any benign sessile or pedunculated growth that projects into the lumen of the intestine. Any of the above-mentioned tumors that project into the lumen are therefore called polyps. Polyps of the intestine may be either single or multiple. Single polyps may occur at any site along the intestinal tract. Adenomatous polyps are found most often in the large intestine, particularly in the rectum. Nonadenomatous polyps, such as fibromata, myomata, lipomata and carcinoids occur most often in the small intestine, especially near the ileocecal junction.

Multiple polyps may vary in number, from a few, scattered isolated polyps to a diffuse type, numbering many hundreds. The most frequent sites of multiple polyps are the rectum, sigmoid, hepatic and splenic flexures of the colon. Most of the reported cases of multiple polyposis of the intestine were of the adenomatous type. Polyps of the adenomatous type may occur in large numbers



FIG. 1.—Multiple fibromatous polyps in the rectum. (Case I.)

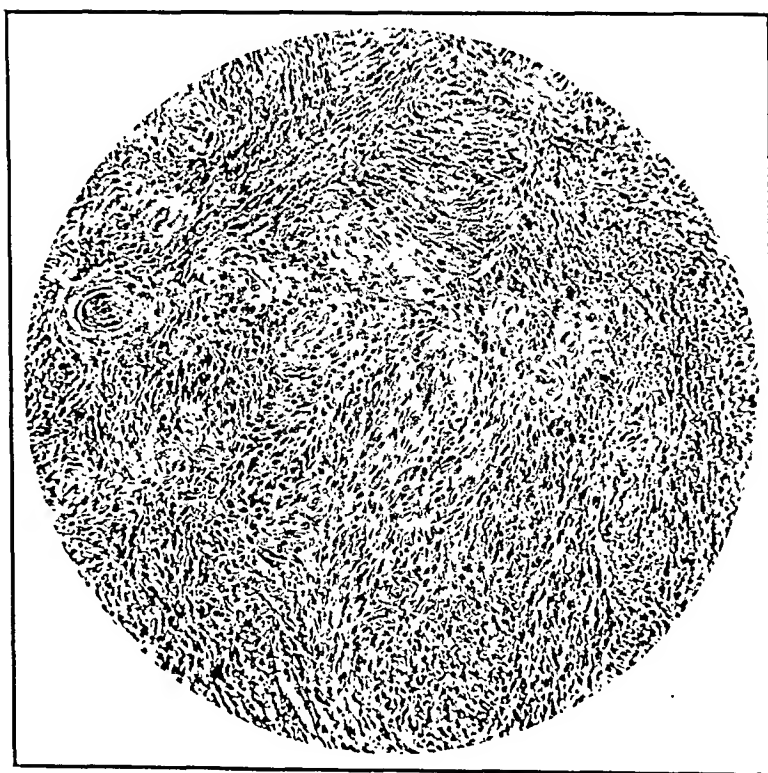


FIG. 2.—Section through a fibromatous polyp of the rectum. (Case I.)



FIG. 3.—Section through a benign adenomatous polyp. (Case II.)

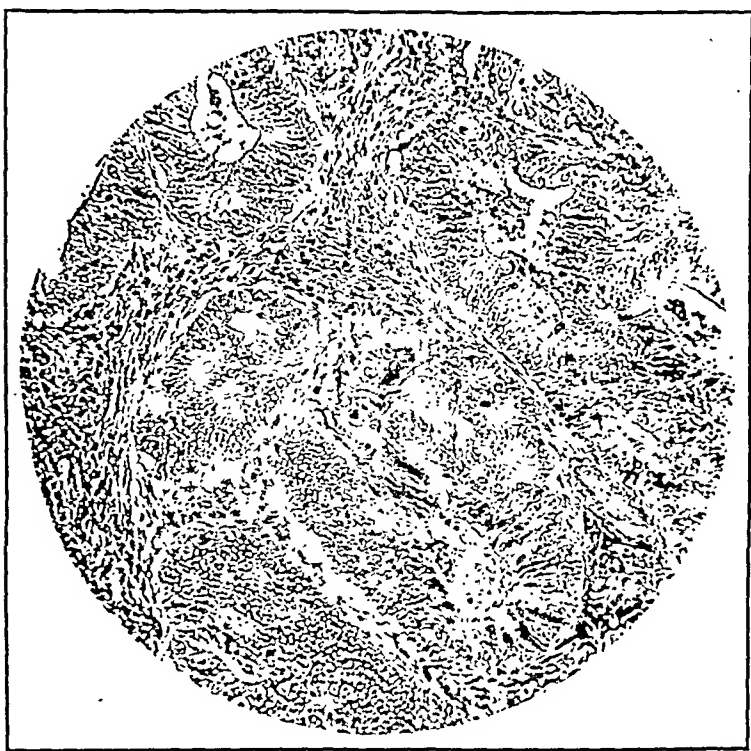


FIG. 4.—Section through an adenomatous polyp undergoing malignant changes. (Case II.)

and in some cases the entire mucosa of the intestine, both small and large, from the pylorus to the anus is studded with countless numbers of tumors, varying in size from a pin-head to a hazel nut. Two cases of nonadenomatous multiple polyposis are recorded in the literature; one, an instance of multiple lipomatosis and one of diffuse myomatosis.

Reviews of the literature on the subject of intestinal polyps are given by Struthers,² Doering,³ Soper,⁴ Erdmann and Morris⁵ and Saint.⁶

Two instances of multiple polyposis are reported in this communication. The first is a case of multiple fibromatous polyposis associated with chronic ulcerative intestinal tuberculosis. We have not been able to find reports of a similar case in the literature.

Case Report. CASE I.—The patient, a middle-aged Russian salesman, was admitted to Montefiore Hospital complaining of attacks of diarrhea recurring at weekly intervals and a loss of 30 pounds in weight during the past two years. For several months prior to admission he had had incontinence of stool, but had not complained of pain or tenesmus. Nine years prior to admission he had been informed that he had hemorrhoids. At that time a routine Roentgen ray film of his lungs showed a "healed" tuberculous focus in one lung.

The patient was pale and emaciated. Evidence of bilateral pulmonary apical tuberculosis was found. On rectal examination, firm, polypoid masses were felt encroaching on the lumen of the rectum. An intestinal Roentgen ray series suggested the diagnosis of a generalized tuberculous colitis with involvement of the small intestine and cecum.

In view of the severe colonic symptoms with obstructive masses in the rectum, an ileostomy was performed by Dr. Gottesman. Pre-operative and postoperative transfusions were given. The patient ran a septic temperature, had a foul-smelling rectal discharge, became intermittently irrational and died seventeen days after the operation.

Laboratory Data: Marked anemia, red blood cells, 2,450,000; hemoglobin, 40 per cent. The blood Wassermann test was negative. The blood sugar and the blood-urea nitrogen were normal.

A Roentgen ray of the lungs showed tuberculous infiltrations in the left lung from the apex to the seventh rib, with evidence of a cavity, 1½ inches in diameter, in the apical region. Posteriorly, infiltrations were present in the right lung from the ninth to the tenth rib.

Autopsy revealed a chronic pulmonary tuberculosis with cavity formation in the left upper lobe, extensive tuberculous ulcerations of the ileum and cecum, multiple fibromatous polyps of the small and large intestines, chronic passive congestion of the liver, arteriolosclerosis of kidneys, ileostomy, chronic maxillary sinusitis.

Rectum (Fig. 1): On opening the rectum, a large number of prominent sessile polypoid bluish-black masses varying in size from 0.5 to 2.5 cm., were seen projecting above the level of the mucosa. These polypoid masses were quite firm in consistency. The intervening mucosa was grayish and fibrotic and only here and there a small island of normal appearing pink mucous membrane was seen. The cut surface of the polypoid masses was grayish-red, firm and extended to the submucosa. The entire wall of the rectum was markedly indurated and thickened. These masses extended as far up as the sigmoid.

Cecum: Showed several small, blackish polyps, some of which were sessile and some of which were pedunculated. The mucous membrane about some of these polyps was extensively ulcerated.

Ileum: From the ileocecal valve, extending for about 30 cm. the ileum was markedly indurated and thickened. The serosal surface showed numerous, partly caseous tubercles of varying size. The peritoneum was markedly injected in this region. The mucosa presented a striking picture. It was greenish-black in color and some areas were a deep blue. There were many raised, indurated, firm, blue-black polypoid projections from the mucosa. The intervening and surrounding tissue showed extensive, crater-like ulcers sharply defined. The mucous membrane between the ulcers was, in places, strikingly thickened and indurated. The remnants of the ileum and jejunum showed scattered, sharply defined moderately large ulcerations. On the serosal surface beneath these ulcers were numerous tubercles. The mesenteric lymph nodes were large and on section densely fibrotic.

Microscopic Examination. *Ileum:* A large portion of the surface mucosa is completely desquamated and covered with a zone of partly necrotic, partly caseous material. In the submucosa, the muscularis and serosa are scattered large tubercles with central caseation.

A Rectal Polyp (Fig. 2): The mucosa is stripped of its surface epithelium. There is a large nodule which protrudes above the line of the normal mucosa. The interstitial tissue of this nodule shows large areas of hemorrhage and on the surface a wide zone of necrosis. The stroma of the polyp consists of very highly cellular tissue that is arranged in whorls and in irregular strands. The cells are fairly regular and spindle shaped. The submucosa is invaded by this stroma. Van Gieson stain identified this cellular tissue as fibromatous. In many of the nodules and in the intervening connective tissue there is evidence of a simple inflammatory reaction.

Comment. It has long been observed that there is a close correlation between chronic irritation and the development of new growths in the intestinal tract. Rokitsky first called attention to the formation of epithelial hyperplasia in islands of mucous membrane in and about scars and cicatrices of healed intestinal ulcers. The association of other forms of chronic irritation with the appearance of new growths has been thoroughly established. Such irritants may be bacterial, chemical or parasitic.

The coëxistence of tuberculosis and new growths has been observed and the possible etiologic relationship has been suggested. It is well known that in the fibrous scars of lungs in tuberculosis, there is often a hyperplasia of alveolar epithelium. Pathologists have noted the appearance of carcinomata in the walls of bronchiectatic tuberculous cavities.

The tubercle bacillus produces a characteristic tissue reaction. Under certain circumstances it is conceivable that islands of epithelial or connective tissue may be stimulated to overgrowth. It is well known that the stroma of the granulation tissue of Hodgkin's disease, for example, may undergo fibromatous or sarcomatous change. In chronic hyperplastic tuberculosis of the intestine adenomatous polyps are frequently observed, but they are limited to areas of stricture formation. It is possible that in the instance reported in this paper the presence of the tuberculous infection played an etiological rôle in the formation of the new growths.

The following instance is one of multiple adenomatous polyposis complicated by intussusception and malignant degeneration of the polyps.

CASE II.—I. B., female, aged thirty-one years, admitted November 18, 1926, for the past fifteen months has noticed mucous and bloody discharge from the rectum at irregular intervals. There were occasional attacks of pain in the left lower quadrant associated with constipation, nausea and vomiting, with radiation to the groin. For sixteen days prior to admission she had no bowel movement and complained of marked nausea and abdominal distention.

Physical examination revealed an acutely sick female, with marked distention of the abdomen, and tympanites and diffuse tenderness over the whole abdomen. On rectal examination, a large pedunculated boggy mass was felt in the posterior wall of the rectum, just within the internal sphincter. Proctoscopic examination showed an ulcerated tumor on the posterior wall of the rectum, extending upward. The upper limit could not be determined. Biopsy was reported adenocarcinoma.

Laboratory Findings: Hemoglobin, 66 per cent; red blood cells, 3,700,000; white blood cells, 30,000; polymorphonuclears, 89 per cent. Other laboratory data negative.

Diagnosis: The pre-operative diagnosis was intestinal obstruction, secondary to adenocarcinoma of the rectum.

Course: A laparotomy was performed (Dr. Gottesman). The entire gut, both small and large, was markedly distended. In the left lower abdomen was found an intussusception of the descending colon into the sigmoid and rectum. Attempts to reduce the intussusception were unsuccessful and simple cecostomy was done.

The patient's condition improved and on December 4 the abdomen was opened, the outer wall of the intussusception was incised, the intussusception reduced and about 18 inches of the sigmoid was removed. The cut ends of the gut were brought into the abdominal wound. (Operation by Dr. Neuhof.)

Pathologic Report: The specimen consists of two segments of colon:

A. Measures 18 cm. long, 12 cm. wide. The wall is uniformly thickened. The mucous membrane is covered with discrete and confluent soft, fleshy globular and flattened elevations varying from a fraction of a millimeter to several millimeters in diameter. The mucous membrane is everywhere intact except at near what appears to be the upper end, where there is an ulceration of the mucous membrane approximately 3 cm. in diameter. The borders of the ulcer are thin and sloping. The base is covered with a thin layer of mucous membrane or hemorrhagic granulation tissue. Along the cut surface of base of ulcer the muscle layer is distorted and replaced by fatty areolar tissue and dense fibrous tissue. At one place the margin of the ulcer is undermined. The base of the ulcer and the overlapping border at this point is covered with a necrotic yellowish-white tissue. The muscle layer throughout is markedly thickened and edematous. (Its firmness suggests possible malignant infiltration.) The peritoneal layer is edematous, thickened and smooth except for small areas in which there are adherent fibrous tags—broken adhesions.

B. Segment is 15 cm. long, about 10 cm. in circumference, one end of which for a distance of 3 cm. resembles the other specimen. Beyond this line there is a sudden increase in the thickness of the wall which is practically uniform and affects the remaining length of the specimen. At the junction of the thick and thin portions, there is no ulceration, the thicker margin is uniformly smooth, the mucous membrane surface being continuous. There is an area of ulceration approximately 3 cm. in diameter at about the middle of the segment. The ulceration involves the muscle layer. The remainder of the inner surface presents a roughened coarsely granular appearance due to elevations similar to those in the other specimen, and in addition is covered over large areas with an adherent thick yellowish-

white membrane; the underlying muscle is similar to that in the other specimen but in places somewhat thicker. The peritoneal surface is similar to that of segment A.

Microscopic examination shows in addition to a marked catarrhal reaction of the mucous membrane, edema of the submucosa and muscle layers and organizing fibrinopurulent exudate on the peritoneal surface. Small areas of mucous membrane are present in which the glands are markedly hypertrophied and irregular, though the basement membrane is intact. These foci of irregular glandular hypertrophy occur on the tips of polypoid-like thickenings of the mucous membrane. In one area the muscle is seen to be invaded by highly irregular glandular structures. A diagnosis of early malignant transformation of multiple polyps with ulceration and chronic colitis was made (Figs. 3 and 4).

Subsequent Course. On June 12, 1927, the cecostomy wound was closed (Dr. Gottesman) and on January 21, 1928, the double-barreled colostomy was closed (Dr. Neuhof). The patient has remained well to date and is entirely symptom free.

Comment. In the preceding instance a long history of chronic ulceratis colitis preceded the appearance of multiple polyposis. It is possible that the long-standing chronic irritation was etiologically related to the formation of the new growths. That intestinal adenomata undergo malignant degeneration is a well-known fact. Various observers estimate that about 40 to 50 per cent of adenomata of the intestine become malignant. Some feel that every case of intestinal carcinoma is preceded by a benign tumor. Mummery traces the various stages in the development of carcinoma from epithelial hyperplasia to adenoma to carcinoma, all following the action of an irritant during a long period of time.

Summary. Two cases of multiple polyposis of the intestine are reported. The first is an instance of multiple fibromata of the small and large intestine associated with chronic tuberculous enteritis. A relation between the chronic irritation and the development of the polyps is suggested. The second instance is one of multiple adenomatous polyps of the intestine complicated by intussusception and malignant degeneration. These two instances again emphasize the etiologic rôle of chronic irritation in the formation of new growths.

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THE INFLUENCE OF MAGNESIUM SULPHATE ON THE SECRETORY ACTIVITY OF THE DIGESTIVE GLANDS.

I. ON THE GASTRIC, INTESTINAL AND PANCREATIC SECRETIONS.

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IN our experiments with magnesium sulphate and the expulsion of bile into the duodenum we were unable to find references to the complete pharmacologic action of this salt on the gastrointestinal tract. The present treatise has to do with the action on the stomach, pancreatic and intestinal secretions, and in a second article we shall summarize our results with the influence of magnesium sulphate on the expulsion and secretion of bile.

1. **Stomach.** In three dogs ("Frant," "Snejok," "Riji"), having Pavlov stomach pouches,* we tried the effect of magnesium sulphate introduced through a gastric tube; and in a fourth dog ("Murzilka") which had both the Pavlov pouch and a gastric fistula we poured the solution directly in through the cannula. The first three dogs had been living in the laboratory for one or more years in good health after the operation, and had been used for other chronic experiments.

Twenty-five to 40 per cent aqueous solution was run in through the stomach tube in "Frant," "Snejok" and "Riji" and allowed to remain. In none of them did we obtain a definite acid secretion. In "Frant" in practically every case there was always within a few minutes nausea and vomiting of a bile-tinged or even a more concentrated biliary secretion mixed with the vomitus. The following is a typical protocol:

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE,
"SNEJOK," JUNE 17, 1925.

12:15—Experiment begun.
12:30—One drop from the little stomach (Pavlov pouch).
12:45—One drop.
12:46—50 cc. of 30 per cent magnesium sulphate solution introduced through the stomach tube.
1:00—0.0 cc. from the little stomach.
1:15—0.0 cc.
1:30—0.0 cc.
1:45—0.0 cc.

* For a complete description of the method of making the Pavlov miniature stomach or pouch, see Babkin (*Die Äussere Sekretion der Verdauungsdrüsen*, Berlin, 1928, p. 180).

In control experiments with water introduced through the tube there was no vomiting and no acid secretion.

TABLE II.—CONTROL EXPERIMENT. "FRANT."

12:15—Brought on the stand.
12:30—0.4 cc. from the little stomach.
12:45—0.3 cc.
12:46—35 cc. of water introduced through the stomach tube.
1:00—0.0 cc.
1:15—0.1 cc.
1:30—0.0 cc.
1:45—0.3 cc.

The results of eleven experiments in "Frant," "Snejok" and "Riji" are given in Table III.

TABLE III.—EFFECT OF MAGNESIUM SULPHATE ON GASTRIC SECRETION FROM THE PAVLOV POUCH. AVERAGE OF ELEVEN EXPERIMENTS.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.15	0.16
Second fifteen minutes	0.13	0.14
Third fifteen minutes	0.10	0.21
Fourth fifteen minutes	0.12	0.10
Total, one hour	0.50	0.51

In "Murzilka" 25 to 80 cc. of a 25 to 35 per cent solution was put in through the gastric fistula, with the dog on its back, allowed to remain in for five minutes, and then drained out while the dog was placed in the supports; in some cases it was allowed to remain in. The collection was made from the little stomach.

TABLE IV.—"MURZILKA," JULY 8, 1927. LAST FEEDING YESTERDAY EVENING.

15:05—On stand; tube inserted; alkaline reaction; stomach washed with 150 cc. distilled water; returned clear; no nausea.
15:31—Alkaline reaction.
15:31-34—50 cc. of 30 per cent magnesium sulphate solution at room temperature introduced through the gastric fistula; 45 cc. was recovered; no retching, etc.
15:36—Alkaline reaction.

	From large stomach.	From stomach pouch.
15:46	12.0 cc.; strongly alkaline	0.2 cc.; alkaline.
16:01	6.0 cc.; alkaline	0.1 cc.; alkaline.
16:16	4.0 cc.; alkaline	0.6 cc.; neutral.
16:17	20	drops bile-colored fluid
16:18	2.0 cc.; saliva	
16:20	Acid.
16:31	5.0 cc.; strongly alkaline (some bile)	0.3 cc.; acid.
16:46	0.5 cc.; alkaline	0.3 cc.; acid.
For one hour	29.5 cc.	1.5 cc.

The results of ten experiments in "Murzilka" are summarized in Table V. Collection was from the Pavlov pouch.

TABLE V.—INFLUENCE OF MAGNESIUM SULPHATE ON GASTRIC SECRETION.

	Average 6 experiments.	Average 4 experiments.
One hr. before $MgSO_4$. .	0.7 cc.	0.15 cc.
	Magnesium sulphate left in for five minutes	Magnesium sulphate left in altogether.
One hr. after $MgSO_4$. .	1.7 cc.	0.44 cc.
Total average . . .	0.49 cc.	1.18 cc.

2. The Local Action of Magnesium Sulphate on the Gastric Mucous Membrane. In two dogs, "Frant" and "Snejok," we washed the little stomach for several minutes with a 15 to 30 per cent solution of magnesium sulphate and determined the rate of flow and the reaction before and afterward. In every one of these experiments except the first the reaction either continued to be alkaline or changed from acid to alkaline.

TABLE VI.—"SNEJOK," JANUARY 6, 1926. THE LOCAL ACTION OF MAGNESIUM SULPHATE (15 PER CENT SOLUTION) ON THE MUCOUS MEMBRANE OF THE STOMACH.

11:40—Dog brought on stand.
13:00—1.2 cc.; acid.
13:15—0.2 cc.; acid.
13:15–20 50 cc. of 15 per cent magnesium sulphate solution run through the Pavlov pouch.
13:20–22—Allowed to drain off.
13:22–28—0.5 cc., neutral.
13:35—0.2 cc, neutral.
13:50—0.3 cc.
14:05—0.0 cc.; mucous membrane is slightly alkaline.
14:20—0.2 cc.; slightly alkaline.

For eighty minutes before the experiments: 1.4 cc.; slightly acid.

For sixty minutes after the magnesium sulphate: 1 cc.; slightly alkaline.

In two other dogs ("Bertha" and "Murzilka"), we introduced the magnesium sulphate directly through the gastric fistula, into the main stomach, allowed it to remain five minutes, drained it off, and then observed the effect on both the large stomach and isolated pouch. The secretion was parallel in the two, that is, the change from acid to alkaline and *vice versa* occurred at about the same time. There was always an alkaline secretion from the stomach. Only once when we used a weak solution of the salt was there an acid reaction. A typical protocol, which also shows the close parallel between the main and isolated stomach, follows:

TABLE VII.—SIMILAR EFFECTS IN STOMACH AND PAVLOV POUCH.

1:30—On stand.		
2:15—Tube inserted.		
2:15—Alkaline.		
2:15-30—0.2 cc.; alkaline.		
2:45-53—Alkaline, Pavlov pouch; large stomach neutral; stomach washed with 400 cc. distilled water, 100 cc. at the time, so as not to distend.		
2:53—Pavlov pouch alkaline; large stomach neutral.		
2:58—Alkaline Pavlov pouch.		
2:47-3:02—0.4 cc.; Pavlov pouch, alkaline.		
3:17—5 cc.; Pavlov pouch, mucoid.		
3:22—Alkaline, both Pavlov pouch and large stomach.		
3:23-28—28 gm. of magnesium sulphate in 56 cc. water (33.33 per cent solution in gastric fistula at room temperature; dog on back; recovered 30 cc. clean colorless fluid; no signs of nausea.		
3:30—Alkaline in both stomach pouch and large stomach.		
	Pavlov pouch.	Large stomach.
3:30-45	0.4 cc.; alkaline	12 cc.; alkaline.
4:00	0.4 cc.; slightly acid	6 cc.; neutral.
4:15	0.3 cc.; slightly acid	2 cc.; very slightly acid.
4:30	0.4 cc.; slightly acid	0 cc.; slightly acid.
4:33-35	2 cc.; green-yellow fluid
	like mixed acid and bile.
4:30-45		3 cc.; acid.
4:45	0.5 cc.; acid.	

We often also obtained bile in the large stomach, accompanied by retching and vomiting. This will be referred to in a subsequent paper. The presence of the alkaline reaction in the isolated Pavlov pouch shows that it could not have been due to the regurgitation from the duodenum.

Our experiments show that magnesium sulphate acts as a weak irritant to the mucous membrane of the stomach. The effect on the gastric secretion was nearly the same whether the magnesium sulphate was allowed to remain in the stomach or was drained out after five minutes.

3. Action on the Intestinal Juice. To determine the effect of magnesium sulphate on the intestinal glands we used three dogs, "Milka," "Achill" and "Zazula," having Thiry-Vela fistulas. In this operation the nerves are intact. "Milka" was operated on one year previously, "Zazula" nine years before and "Achill" two years before. In "Zazula" the loop of gut came from the duodenum and upper jejunum, while in the other two dogs it was from the jejunum. (For complete description of the operation see Babkin: "Die äussere Sekretion der Verdauungsdrüsen," Berlin, 1928.) The magnesium sulphate solution, 25 to 30 per cent was run through in a stream for five minutes, allowed to flow out, and then the fluid collected in an attached graduate, measured every five minutes.

Table VIII shows that the secretion after introduction of the magnesium sulphate is much greater than before. Control solution of physiologic saline run through in the same way as the magnesium sulphate was, without effect.

TABLE VIII.—EFFECT ON INTESTINAL SECRETION. "ZAZULA," APRIL 17, 1925.

11:55—On stand.
12:00—0.1 cc.
12:05—0.1 cc.
12:10—0.0 cc.; 0.2 cc.
12:15—40—0.0 cc.
12:40—45—20 cc. warm 30 per cent magnesium sulphate (38°) and allowed to drain five minutes.
12:55—1.0 cc.
1:00—0.5 cc.
1:05—1.6 cc.; 3.2 cc.
1:10—2.6 cc.
1:20—0.2 cc.; 2.8 cc.
1:25—0.0 cc.
1:30—0.0 cc.
1:35—0.0 cc.; 0.0 cc.
1:45—0.0 cc.
2:00—0.0 cc.; 0.0 cc.

TABLE IX.—SUMMARY OF NINE EXPERIMENTS SHOWING EFFECT OF MAGNESIUM SULPHATE ON INTESTINAL SECRETION.

	Before magnesium sulphate, cc.	After magnesium sulphate, cc.
First fifteen minutes	0.05	1.8
Second fifteen minutes	0.15	1.2
Third fifteen minutes	0.5
Fourth fifteen minutes	0.3
Totals:		
One-half hour	0.20	
One hour	3.9

4. Action on the Pancreatic Secretion. We tried the effect on the pancreatic secretion by injecting the magnesium sulphate solution through a tube into the stomach in dogs with permanent pancreatic fistulæ. The results of four experiments are summarized in Table X.

TABLE X.—AVERAGE OF FOUR EXPERIMENTS IN TWO DOGS, SHOWING EFFECT ON PANCREATIC SECRETION.

	Before injection, cc.			After injection, cc.			
	First 15 min.	Second 15 min.		First 15 min.	Second 15 min.	Third 15 min.	Fourth 15 min.
First experiment	0.2	0.2	Magnesium sulphate (30 per cent) injected in- to stomach	1.4	1.6		
Second experiment	0.5	0.6		2.0	0.5	0.6	1.9
Third experiment	0.5	0.0		0.3	0.2	0.6	0.9
Fourth experiment	0.6	0.3		0.3	0.7	3.0	0.8
Average	0.4	0.3		1.0	0.8	1.4	1.2

These experiments are too few to admit of definite conclusions, nor is it possible to say, without further experimentation, how much of the action is due to the water and to the passage of the tube.

In our protocols the pancreatic juice was somewhat increased

for the first hour after injection. It has been shown in Pavlov's laboratory that water* in the stomach is an independent exciter of the pancreatic juice, that is, it has an action in addition to that of the hydrochloric acid which it also calls forth.

Summary. A 30 per cent magnesium sulphate solution acts in the stomach as a mild irritant, producing a very small flow, which is usually alkaline. In a few experiments with the pancreatic secretion there was a slight increase in the pancreatic juice, which began immediately after giving the magnesium sulphate through the stomach tube. There is, however, a copious secretion of the intestinal glands all along the small gut, produced by the local contact of magnesium sulphate with isolated loops of gut. This occurred in the upper and lower duodenum as well as in the ileum and jejunum.

NOTE.—We desire to thank Prof. V. V. Savitch, of Leningrad, and Dr. Babkin, of Montreal, for suggestions regarding these experiments.

* The other independent exciters of the pancreatic flow are acid, fat and its products, and bile.

THE INFLUENCE OF MAGNESIUM SULPHATE ON THE SECRETORY ACTIVITY OF THE DIGESTIVE GLANDS.

II. ON THE BILIARY SECRETION.

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IN the first paper of this series we showed that magnesium sulphate caused a great flow of intestinal juice, but that it had very little effect on the stomach, and probably but little on the pancreatic secretions.

The results of our experiments in six dogs having various operations on the digestive tract, to be described in the present article, show that magnesium sulphate introduced whether into the stomach or directly into the duodenum has no specific action on the expulsion and secretion of bile.

We previously described the failure to obtain expulsion of bile into the duodenum on the introduction of magnesium sulphate directly into the duodenum through a cannula in a dog having a fistula of the gall bladder.¹

The next dog, "Sharik," had a choledochus fistula after the method of Pavlov.² In this operation the end of the choledochus and surrounding mucous membrane of the duodenum containing the papilla of Vater is brought out on the skin and the duodenum closed. Thus all the secretion of bile has an external flow. We

performed seven experiments altogether in "Sharik" with magnesium sulphate, introducing 25 to 40 cc. of a 30 per cent magnesium sulphate solution through the stomach tube. There was no flow of bile for the first hour in any of these experiments, but in two of them a small amount was expelled during the second hour. In the only case in which we saw a noteworthy expulsion of bile, retching and nausea occurred, a little bile was expelled simultaneously, and a considerable amount the second hour. Control experiments of meat produced a flow; and alkaline mineral water caused an average expulsion of 6.2 cc. for the first hour, and 4 cc. for the second hour, but distilled water was without effect.

Two protocols follow:

TABLE I.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO STOMACH ON EXPULSION OF BILE.

"SHARIK," JULY 24, 1925.

12:45—0.0 cc.
 1:00—0.0 cc.
 1:15—0.3 cc.; thin yellow.
 1:30—0.0 cc.; 0.3 cc.
 1:45—0.0 cc.
 2:00—0.0 cc.
 2:15—0.0 cc.; 0.0 cc.
 2:22—25 cc.; 30 per cent magnesium sulphate at room temperature through stomach tube.
 2:30—0.0 cc.
 2:45—0.2 cc.; at 2:40 retching, and attempt to vomit; bile only after retching.
 3:00—0.0 cc.
 3:15—0.0 cc.; 0.2 cc.
 3:25—Begins to drop.
 3:30—0.2 cc.; yellow-brown.
 3:45—1.2 cc.; yellow-brown.
 4:00—1.0 cc.; yellow-brown.
 4:15—1.4 cc.; yellow brown; 3.8 cc.
 4:30—2.0 cc.; yellow-brown.
 4:45—0.5 cc.; yellow-brown.
 5:00—0.2 cc.; yellow-brown.

"SHARIK" AUGUST 8, 1925.

11:10—On stand and duct probed.
 11:30—0.0 cc.
 11:45—0.0 cc.
 12:00—0.0 cc.
 12:15—0.0 cc.; 0.0 cc.
 12:20—22—43 cc.; 30 per cent magnesium sulphate about 43° C. through stomach tube.
 12:30—0.0 cc.
 12:45—0.0 cc.
 1:00—0.0 cc.
 1:15—0.0 cc.; 0.0 cc.
 1:30—0.0 cc.
 1:45—0.0 cc.
 2:00—0.0 cc.
 2:15—0.0 cc.; 0.0 cc.
 2:16—19—200 gm. fine raw beef, well mixed, 200 gm. distilled water.
 3:30—0.0 cc.
 2:35—Bile begins.
 2:45—1.0 cc.
 3:00—1.8 cc.
 3:15—2.4 cc.; 3.2 cc.

From this series of uniform experiments it is quite evident that the magnesium sulphate in the stomach caused no effect whatever on the expulsion of bile with the exception of the single instance in which retching and nausea occurred.

In the second dog, "Ajax," the magnesium sulphate was put in directly through a duodenal fistula, the papilla of Vater having been left in its normal position. The operation had been done a month before the experiments, and a cannula inserted into the duodenum. We performed two experiments in this dog, running in magnesium sulphate for five minutes and then allowing it to drain out. In neither experiment did we get a definite spurt of bile, though there was such a spurt after milk was given. There was a marked flow of alkaline duodenal juice, but it contained very little bile.

TABLE II.—EFFECT OF INTRODUCTION OF MAGNESIUM SULPHATE INTO DUODENUM. "AJAX," OCTOBER, 7, 1925.

10:15—9 cc.; golden-yellow bile, coming in spurts, sometimes cloudy.
10:25—18 cc.; 27 cc.
10:30—6 cc.; light amber.
10:35—3 cc.; light amber.
10:40—5 cc.; 14 cc.
10:45—3 cc.; light straw.
10:50—0 cc.
10:55—1 cc.; yellow; 4 cc.
11:00—0 cc.
11:05—0 cc.
11:10—0 cc.; 0 cc.
11:10—25 cc.; 30 per cent magnesium sulphate run in for five minutes through fistula, allowed to run out; 13 cc. yellow bile-colored fluid obtained.
11:20—11 cc.; yellow (duodenal juice).
11:25—3 cc.; straw color.
11:30—11 cc. dirty straw; 25 cc.
11:35—4 cc.; straw.
11:40—6 cc.
11:45—3 cc.; 13 cc.
11:50—0 cc.
11:55—0 cc.
12:00—0 cc.; 0 cc.
12:05—25 cc. milk given just as magnesium sulphate (allowed to remain five minutes, and then run out 10 cc. returned).
12:10—
12:11—Bile appears; 5 cc. milk.
12:15—3 cc. acid.
12:19—3 spurts of pure bile.
12:20—1 cc.
12:25—4 cc.; 8 cc.

The third dog, "Spot," had a stomach fistula and also the chole-dochus fistula after Pavlov as in "Sharik." The dog was turned on its back and 25 to 40 cc. of magnesium sulphate at room temperature run into the stomach, and allowed to remain there. In two experiments, after a latent period of three minutes a definite flow of darker bile set in. In the other two experiments, there was no expul-

sion of bile whatever for an hour after the injection. This expulsion of bile may have been due to the coincidence with the periodic secretion or something in the procedure.

In two other dogs, "Murzilka" and "Frant," we introduced magnesium sulphate through the stomach tube. "Frant" vomited every time and in each instance the vomitus was bile colored. "Murzilka" had a gastric fistula, and we could observe the contents of the stomach. It seems significant that in five of the six experiments there was no regurgitation of bile and no retching or nausea, and that in the single case in which more than a trace of bile was present there was retching.

Effect on the Secretion of Bile. In one dog, "Tulpan," which had a gall bladder fistula with the choledochus tied so that all the secretion could be collected and measured, we introduced 50 to 70 cc. of 30 per cent magnesium sulphate solution through the stomach tube, and allowed it to remain. The quantities before and after introduction are shown in the following table.

Control experiments of distilled water and of alkaline mineral water had little or no effect on the amount of bile secreted. (Experiments of Drs. Geffer and Martinson.)

TABLE III.—CONTROL EXPERIMENTS (DISTILLED WATER AND ALKALINE MINERAL WATER.) AVERAGE OF SIX EXPERIMENTS.

	Bile excreted.
Two hours before injection	7.5 cc.
One hour before injection	4.2 "
Two hours after injection of magnesium sulphate in stomach	9.5 "
One hour after injection of magnesium sulphate in stomach	6.6 "

Although this seems to indicate a slight effect on the amount of bile secreted, the material we have is not enough to be conclusive.

We feel we can state with assurance, however, that in the dog, 30 to 40 per cent magnesium sulphate solution introduced either directly into the stomach or the duodenum has no effect on the expulsion from the gall bladder. In the few cases when bile appeared it could be explained by the nausea and retching. Frazer⁷ found after injecting magnesium sulphate into the duodenum no increased secretion of bile from a choledochus fistula, though he employed a slightly different operative technique from ours.

Summary. My own clinical experience, as well as that of Lyons, Friedenwald and other prominent gastroenterologists, showed that there was very often a flow of bile from both the biliary passages and gall bladder after magnesium sulphate introduced through a stomach tube. Subsequent experimental work on dogs in which the magnesium sulphate was put directly into the duodenum rarely produced bile and never any increase of pressure in the gall bladder. In other dogs in which we gave the magnesium sulphate by mouth

through a tube, bile was usually secreted; but some of these animals never reacted in this way. Finally in another dog in which we ran the magnesium sulphate directly into the stomach through a fistula we sometimes got bile regurgitated and sometimes did not.

Reviewing our results, we found that the dog in which we always obtained bile was one which always had nausea and vomiting after the magnesium sulphate, those which never gave bile never had nausea and vomiting after the procedure; and in the one in which we sometimes found bile and sometimes did not, whenever there was bile it was preceded by nausea and vomiting and when there was no nausea and vomiting there was no bile.

This reconciled our own clinical and laboratory results in man and in dogs, and, furthermore, we think clears up much of the mystery of magnesium sulphate which has lasted for a decade. It is quite likely that magnesium sulphate may cause a contraction of the duodenum (Auster and Chron, Diamond, Kawashima), and a local relaxation of the sphincter of Oddi, and under these conditions if there is nausea or vomiting, which may quite readily be produced by the passage of the tube alone or by the injection of substances into the duodenum, or under other conditions bringing about expulsion from the gall bladder as shown by Winkelstein, there may follow expulsion of bile from the bladder into the duodenum. We must remember that a large number of other substances in the duodenum also produce a flow of bile, and that bile enters the duodenum periodically.

Recently an assistant of Pavlov, K. M. Bykov,¹⁰ has shown that conditioned reflexes may play a part in the secretion of bile, and moreover that this secretion may be an enteroreceptory one (that is, from the internal nerves) instead of an extero-receptory one (as for example from the eye, ear, skin).

If this is so—that even so complicated a process as the secretion of bile may be conditioned, then it is quite clear that if there were (as there usually is in most patients) nausea and vomiting from the introduction of the duodenal tube and the magnesium sulphate, once or several times, with the expulsion of bile, the flow might subsequently become conditioned to the method of the procedure even though the nausea failed to appear. The nausea and antiperistalsis could thus explain the expulsion of bile occurring the first times, and it seems quite likely in view of Bykov's experiments, that later, in those patients who are drained often, there might be a conditioned flow elaborated which is analogous to that of Pavlov's conditioned reflex.*

* Bile (unconditioned stimulus) was injected into the blood and there followed an increase of the bile secretion (unconditioned reaction). This procedure was repeated a good many times. Later on, merely putting the dog on the stand and making the necessary preparations for the injections (conditioned stimulus) proved sufficient to increase the biliary secretion (conditioned reaction).

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A NEW NEEDLE GUARD AND GUIDE FOR PARAVERTEBRAL NEURONE BLOCK INJECTIONS.

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IN certain conditions of great pain, such as in severe angina pectoris, herpes zoster, meralgia paresthetica, tabetic crisis and so forth, it is sometimes necessary to infiltrate the spinal nerve roots in the thoracic region with different medicines. This procedure

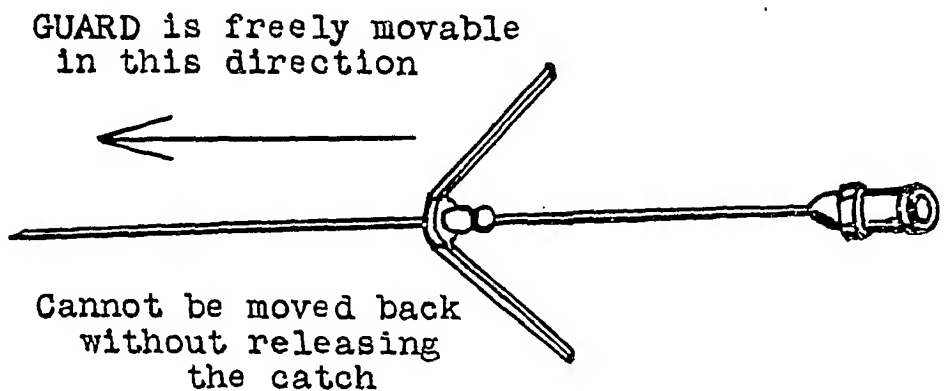


FIG. 1.—Needle guard and guide for paravertebral neurone block injections.

has also been used for the immediate relief of severe pain associated with cancerous growths in the thoracic cavity and its walls, as well as in paravertebral spinal anesthesia.

The proper insertion of a hypodermic or long spinal needle into

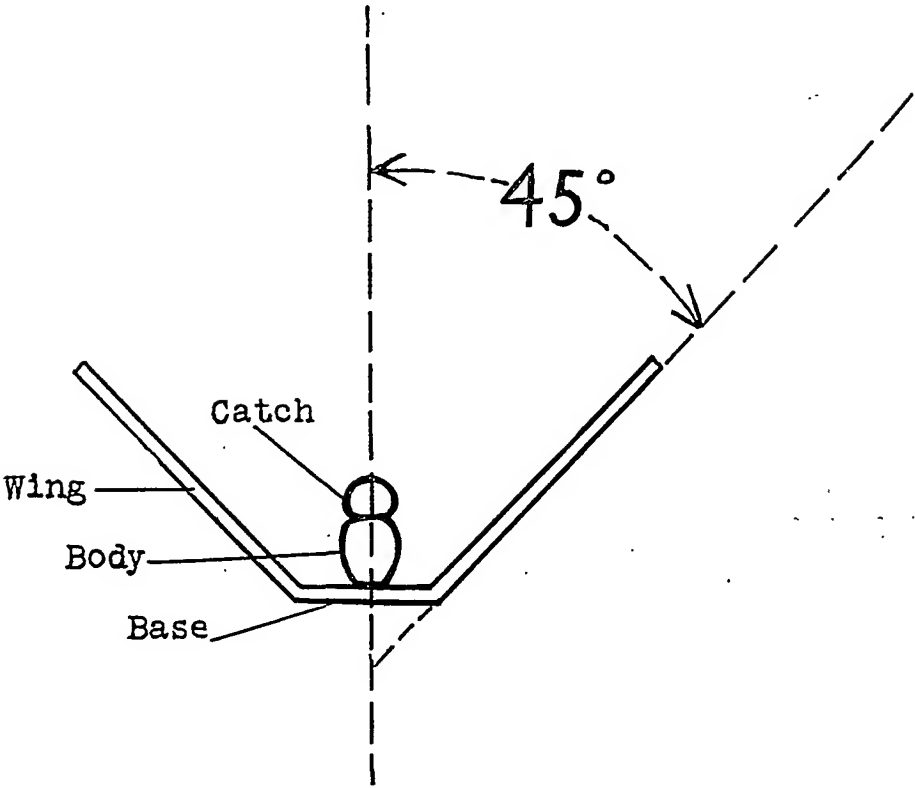


FIG. 2.—Needle guard and guide for paravertebral neurone block injections.

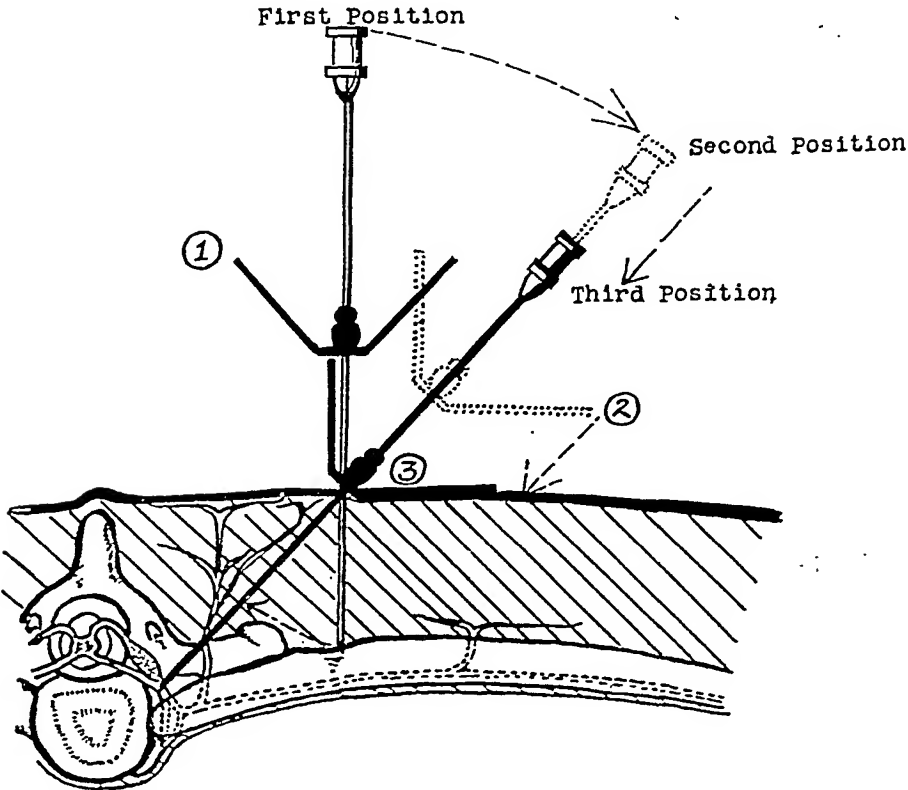


FIG. 3.—Diagram of spinal nerve, showing how the instrument localizes the posterior root.

the desired area is one of extreme difficulty, not only because of the bony impediments offered by the spinal column and the thoracic

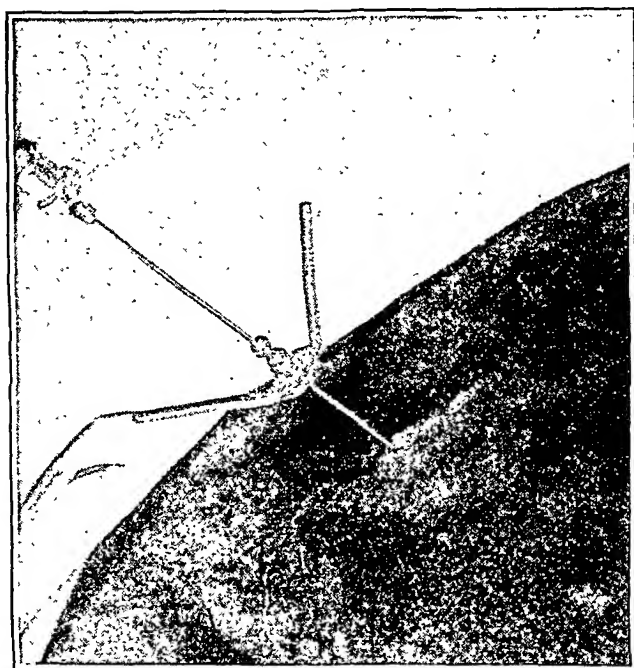


FIG. 4.—Patient lying on side. Needle in first position; diagrammatically shown in Fig. 3.

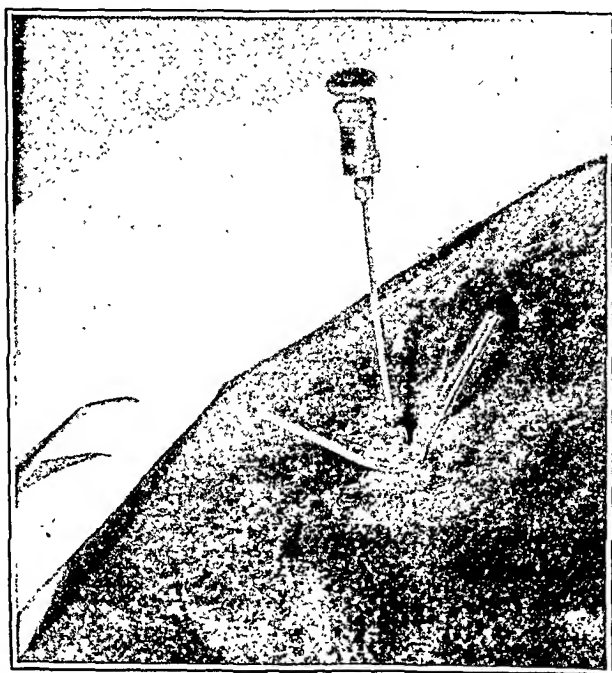


FIG. 5.—Needle in third position; diagrammatically shown in Fig. 3.

framework, but also because of the ever-present danger accompanying injury of vital structures.

The device here offered to overcome any difficulty and danger consists of an adjustable guard placed on the needle, and held there in such a manner that it can easily be moved away from the hub, but not toward it (Fig. 1). This is accomplished by a special catch which holds the guard on the shaft of the needle. The wing of the guard (Fig. 2) has an inclination of 45 degrees with the base of the guard.

To use the guard for paravertebral work, insert the needle perpendicularly to the surface of the back, about 4 cm. from the spinous processes, until you hit the lower margin of the rib above the nerve root to be injected. Then adjust the guard (Fig. 3, 1) to a distance of 2 cm. from the surface of the skin, which distance is also equal to the *length* of the wing. Then slightly withdraw the needle, and tilt it sufficiently to make the wing parallel to the surface of the body (Fig. 3, 2). This will bring the needle to an inclination of 45 degrees. Now push the needle in, at this inclination, until the guard hits the skin, thus preventing it from going any further (Fig. 3, 3). The needle will then be in position for the injection.

BRONCHIECTASIS.

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Incidence. Even though no exact figures are given in the textbooks on medicine and surgery concerning the incidence of bronchiectasis, the impression is left that this condition of chronic pulmonary disease is relatively rare, certainly much less frequent than pulmonary tuberculosis. Lord¹ states that there were only 38 cases among 3183 autopsies at the Boston City Hospital. Undoubtedly bronchiectasis, with marked anatomic change in the bronchi, as found at autopsy in advanced cases, is relatively rare. That bronchial dilatation, however, is not rare has been repeatedly shown since the introduction of methods by which the tracheo-bronchial tree may be visualized. From the author's personal experience, he is forced to conclude that bronchiectasis is the most frequently encountered chronic pulmonary affection, occurring even more frequently than pulmonary tuberculosis. That many cases of bronchiectasis, nontuberculous in nature, are being diagnosed and treated as tuberculosis at the present time has been definitely shown. That such errors have been made is easily understood. A patient with a persistent cough lasting over a period of years, which resists all forms of therapy, has in the past been considered tuberculous, even though the sputum has been repeatedly negative.

Such an individual has been given the "benefit of the doubt," and has been referred to a tuberculosis sanitarium. From 25 to 50 per cent of all inmates of tuberculosis sanatoria are nontuberculous (Hamilton²). That bronchiectasis may be caused by tuberculosis must not be forgotten, but this type of bronchiectasis is relatively rare as compared with the nontuberculous type.

Etiology.—The etiology of bronchiectasis is varied. Many conditions have been blamed for the pathologic changes occurring in the bronchi. A fetal bronchiectasis was first described by Grawitz,³ who contended that bronchiectasis was the result of congenital cystic changes in the lung. Sauerbruch⁴ is a recent champion of the congenital theory. Duken⁵ believes that a few cases of bronchiectasis are congenital. He considers that the predisposition to bronchiectasis is congenital, as bronchiectasis is often associated with other congenital abnormalities, such as idiocy and imbecility. Henschen⁶ and Willy Meyer⁷ consider a congenital malformation as a possible cause of bronchiectasis.

Cirrhosis of the lung was considered the cause of bronchiectasis first by Corrigan.⁸ Since this time Henschen,⁶ Meyer,⁷ Kaufmann,⁹ Schott,¹⁰ Steinmeyer and Kathe,¹¹ Duken,⁵ and Findlay and Graham¹² believe that cirrhosis of the lung may play an etiologic rôle. Chronic pneumonia has been mentioned as a cause of bronchiectasis by Henschen,⁶ Findlay,¹³ and Adams.¹⁴ Hedblom,¹⁵ Meyer⁷ and Waetjen¹⁶ believe that in bronchiectasis there is an alteration in the bronchial gland mucous secretion which, normally, is bactericidal. The secretion, having lost its bactericidal property, permits the growth of organisms. As a result of this infection there is weakening of the bronchial wall, allowing dilatation to occur. Duken¹⁷ is of the same opinion.

That acute infectious diseases may be the cause of bronchiectasis has been shown by Duken,⁵ Elliott¹⁸ and Graham.¹² Opie and his coworkers¹⁹ and Mikulowski²⁰ state that of the various acute infections influenza, pertussis and measles occur most frequently as causative agents in bronchiectasis. Of these, influenza undoubtedly occupies first place, as the incidence of bronchiectasis has increased considerably since the 1918-1919 pandemic of influenza.

Attention has been called to the fact that chronic sinusitis is usually associated and may be the cause of bronchiectasis in a large percentage of cases. Rist,²¹ in 1916, first demonstrated the association between chronic coughs and sinusitis. More recently the etiologic rôle which sinusitis plays in bronchiectasis has been stressed by Mullin,²² Webb²³ and Adams.²⁴ Sinusitis is such an important cause of bronchiectasis that the possibility of a bronchiectasis developing in every persistent case of sinusitis must be considered.

The loss of nerve control of the bronchi is considered by Lebert²⁵ and Biermer²⁶ to be a cause of bronchiectasis. Stenosis of the bronchi, producing obstruction to the outflow of air, is considered

as a cause of bronchiectasis by Schott,¹⁰ Franke,²⁷ Sauerbruch⁴ and Kaufmann.⁹ The obstruction may be the result of a congenital narrowing, an inspired foreign body, or a neoplasm. In all cases of bronchial stenosis a bronchial dilatation occurs distal to the obstruction, but obstruction is probably a *relatively* infrequent cause of bronchiectasis.

Of all the various causes of bronchiectasis, the one most frequently responsible for the condition and, therefore, the one most important is a chronic inflammatory process involving the bronchi, that is, chronic bronchitis (Andral,²⁸ Stokes,²⁹ Findlay and Graham,¹² Sauerbruch,⁴ Kaufmann⁹ and Duken⁵). In the author's experience bronchitis is by far the most frequent cause of bronchiectasis. In a series of young University students suffering from chronic bronchitis or attacks of acute bronchitis, giving no clinical evidence of bronchiectasis, a definite bronchial dilatation was found in over 90 per cent.³⁰ Brauer³¹ considers early stages of bronchiectasis as arrested catarrhs in the lower lobes of the lung.

Pathologic Anatomy.—In postmortem and lobectomy specimens certain characteristic pathologic findings can be demonstrated in bronchiectasis. As the name implies, the bronchi are dilated. There are three main types of dilatation: (1) the cylindrical; (2) fusiform; (3) saccular. Sauerbruch⁴ believes that it is possible to differentiate between the first and last of these types etiologically, as he considers the sacculated variety a congenital anomaly, whereas the cylindrical variety is usually the result of inflammatory change. Dilatation may occur in the bronchi, bronchioles or both. The mucosa lining the bronchi may either be hypertrophic or atrophic. In the early stages, there is usually hypertrophy, whereas later atrophy occurs. In the hypertrophic areas papillomatous growths may occur, which are exceedingly vascular. Sauerbruch⁴ states that the inflammatory process begins first as a catarrhal swelling in the mucous membrane with a marked cellular infiltration. The smoothness of the bronchial mucosa disappears. There is often hypertrophy of the entire wall of the bronchus. The mucous glands, the cartilage and the peribronchial structures are enlarged. There is calcification of the degenerated portions, especially in the region of the cartilage. Because of the mucosal involvement there is a diffuse purulent secretion. The epithelium may be intact or may be desquamated, resulting in ulceration from which hemorrhage is apt to occur. In the advanced stages of the atrophic form, the bronchial musculature and elastic fibers, as well as the mucous glands, and even cartilage, are destroyed, the entire wall being replaced by fibrous tissue. In these advanced forms, the pulmonary tissue surrounding the bronchi shows definite changes, such as fibrosis and atelectasis. These pathologic findings in the lung and the bronchi, which are well known to all pathologists, represent, however, the late stages of the condition, bronchiectasis. The

author is of the opinion that by far the greater number of cases of bronchial dilatation seen, and clinically improved by the introduction of iodized oil into the tracheobronchial tree, have relatively little anatomic change in the bronchial wall. In four personally observed cases in which, both clinically and radiographically, bronchiectasis was definitely diagnosed, not only the clinical symptoms were relieved following the introduction of adequate therapy, but also the radiographic evidence of bronchiectasis disappeared. In these patients, bronchiectasis, in an anatomic sense at least, did not exist. In all probability a functional dilatation of the bronchi precedes any anatomic change. This dilatation probably is caused by atony of the bronchial musculature, which has been acted upon by bacterial toxins, aided by stagnation of retained secretions. No definite period is required for anatomic changes to occur, which may appear either after short or long intervals. The lower lobes are by far the most frequently involved, the left more frequently than the right. According to Sauerbruch,⁴ the left lower lobe is involved in from 80 to 95 per cent of all cases. The condition may be found, but is relatively rare in the upper lobe; in fact, it is questionable whether a nontuberculous bronchiectasis ever occurs in an upper lobe without there also being an involvement of the lower lobes. The reason the lower lobes are most frequently involved is probably because of the stasis of the retained secretion. The reason the lower left lobe is more frequently involved than the right is not known. Sauerbruch⁴ believes that as a result of a congenital malformation there is more apt to be obstruction in the left bronchus than in the right. Duken⁵ is of the opinion that the left lower lobe is involved more frequently than the right, because the left bronchus comes off the trachea at a more acute angle than the right and because the pulmonary artery crossing on the left produces a slight constriction of the left main bronchus just before the upper bronchus is given off. The lesions are bilateral in over half of the cases.

Symptoms and Signs.—The clinical picture, as described in most of the textbooks on medicine and surgery undoubtedly represents a late stage of the condition. If one waits until the patient presents a picture of marked pulmonary suppuration, considerable time will be lost. While undoubtedly there are many cases of such advanced stages of bronchiectasis, these are much less frequently encountered than the early, less advanced cases. The clinical picture often described is as follows: A patient who has had an antecedent pulmonary infection expectorates large amounts of fetid sputum, varying from a few cubic centimeters to 1000 or more cubic centimeters in twenty-four hours. The expectoration is often described as being "mouthful" in type, that is, the patient, following a paroxysm of cough, will bring up a mouthful of sputum. This is associated with fever, anorexia, and loss of weight. There are, however, late symptoms. The early symptoms and signs of bronchiectasis, and those

which occur at the time a diagnosis should be made so that the proper therapy might be instituted, are relatively insignificant. The author found in a group of apparently normal young university students, who complained of persistent cough or recurrent attacks of cough, either associated with or without sputum, and in whom a diagnosis of chronic bronchitis had been made, a definite bronchial dilatation in 92 per cent of the cases. The diagnosis in each case was made bronchographically. Some of these patients had no sputum, representing the "dry bronchiectasis" of Bezançon;³² others had a cough associated with a slight amount of sputum, usually present only when the patient suffered from an acute respiratory infection. The sputum in this type of case is rarely fetid, although at times it may have a slightly unpleasant odor and taste. Except in the case of "dry bronchiectasis," the effect of posture on the cough and sputum has been almost invariably noted. Patients often find that by assuming certain positions, especially at night, the cough and expectoration are apt to be aggravated. This depends upon the mechanical drainage of the bronchioles allowing the retained secretion to enter the more sensitive portions of the bronchi, which induces coughing. Early in bronchiectasis the cilia of the bronchial mucosa are lost, permitting a stagnation of the secretion in the terminal bronchi and bronchioles.

Hemoptysis is a frequently encountered symptom, being present in from 50 to 70 per cent of cases. Seldom is bleeding severe; very frequently, however, a tinging of the sputum with blood is noted. Clubbing of the fingers is present only in the advanced cases and those in which the condition has existed for a long period of time. Except in advanced cases, the patient feels well, aside from some slight lassitude. They often complain of not having the amount of energy which they usually have, although they are able to perform their work comparatively well. Because of rather vague, indefinite symptoms, these individuals are often branded as neurotics. Such a patient has been described in detail in a previous publication by the author.³³ In 25 cases reported by Findlay¹³ cough was present in 24 and absent in 1. Expectoration was present in 17 and absent in 6. In 50 per cent of Elliott's¹⁸ cases a previous diagnosis of bronchitis had been made. In all probability bronchiectasis was present at the time the diagnosis of bronchitis was made. Fever and chills are relatively rare in bronchiectasis and in the early cases are practically never encountered. That bronchiectasis may occur with relatively few signs and symptoms was shown by Duken.⁵ "We have discovered bronchial dilatation by means of the filling procedure (bronchography) in cases in which clinical findings showed nothing more than a slight bronchitis and in which the history completely failed."

The physical findings in bronchiectasis also vary. In by far the majority of cases and in all of the early cases the physical findings

are minimal. Almost invariably, however, there is some lagging on the affected side, especially at the base. Characteristically, there is no change in the percussion note except in the late cases. Diaphragmatic excursion is usually normal. Auscultation reveals relatively little, although moist râles, which persist after coughing, are usually audible at the base of the lung. These are not infrequently localized in a relatively small area, and special care must be taken in order to detect them. In the advanced cases marked limitation of motion is present; there is impairment of resonance over the affected lobe, due to an associated pneumonitis; moist, bubbling râles are audible; bronchial breathing is present. In advanced and long-standing cases of bronchiectasis there is flattening of the affected side of the chest, due to the pulmonary cirrhosis, and there may be some curvature of the spine. Pulmonary osteoarthropathy is present in most of the cases in which the condition has existed for a long period of time.

Diagnosis.—Before the use of iodized oil as a contrast substance, the diagnosis of bronchiectasis was made on the history, physical findings, and, occasionally, by means of the Roentgen ray plate. It was then not difficult to diagnose the advanced cases with their typical history and physical findings. The Roentgen ray was of value in those cases in which bronchiectasis was marked and when the process was limited to the right side. As in the majority of cases of bronchiectasis the pathologic process is limited to the left side, it is evident that a roentgenogram was of limited value, because the cardiac shadow obscures the lung parenchyma and bronchi.

With the introduction of lipiodol by Sicard and Forestier,³⁴ in 1922, as a contrast substance, it became possible to visualize a tracheobronchial tree by means of the Roentgen ray and thus demonstrate any deviation from the normal outline of this system. The procedure became quite popular and was valuable in confirming the clinical diagnosis of bronchiectasis in those patients presenting typical clinical signs and symptoms of the condition. At the present time it is generally accepted that a diagnosis of bronchiectasis should not be made unless positive roentgenographic evidence is obtained following the introduction of a contrast substance in the tracheobronchial tree. The greatest value of bronchography is, however, not sufficiently appreciated at the present time. Even before the introduction of iodized oil, it was not difficult to diagnose the advanced case of bronchiectasis. These cases can be correctly diagnosed at the present time without the use of bronchography, even though the extent and exact location of the process may be difficult to determine without it.

Bronchography is of special value, however, in the early, relatively mild cases in which the symptoms are minimal, such as those cases of bronchiectasis in which cough, with or without expectoration is the only symptom. The diagnosis which is usually made in these

cases is chronic bronchitis or recurrent acute bronchitis. If much is to be accomplished in the treatment of bronchiectasis, it is necessary that the diagnosis be made early. In the group of university students referred to above, there were neither symptoms nor signs suggestive of the true pathologic lesion. The only symptom present in most of these cases was cough. In all a diagnosis of chronic bronchitis had been made. Two of these cases have been described in detail in a previous publication.³³ In performing a bronchography it is essential, in order to avoid an error in diagnosis, that the fluoroscopic observation of the mode of filling of the bronchi be made. This is one of the most important factors in making a correct diagnosis, because of the possibility that the iodized oil may pass into the alveoli and produce such a haziness that the bronchi may be obscured. The author has observed 6 cases in which a diagnosis of bronchiectasis was very definite during the first few minutes following the introduction of the contrast substance into the tracheobronchial tree. A roentgenogram of the chest, made about sixty seconds later, showed the outlines of the bronchi so obscured by oil in the alveoli that it was impossible to detect any bronchial dilatation. The importance of the fluoroscopic observation of the mode of filling of the bronchi, in order to prevent a false impression being obtained as a result of two bronchi being superimposed upon one another, has been emphasized by Lenk and Haslinger.³⁵

Treatment.—The treatment of bronchiectasis in the past has been both medical or conservative and surgical or radical. Because, however, the medical treatment has been more or less unsatisfactory and yielded relatively few results, surgery in bronchiectasis has been much more frequently employed. To quote Whittemore,³⁶ "Medical treatment may be dismissed by saying that it cannot cure any case, although, if the patient can devote his life to taking care of his health, spending his winters in a dry, warm climate, using postural drainage, it may be that he will live a long and fairly comfortable life. There is no drug that has any definite influence in curing the disease." On the other hand, Sauerbruch⁴ states, "The surgical treatment of bronchiectasis is certainly the hardest and least thankful chapter of the entire lung surgery."

The surgical treatment of bronchiectasis dates back to 1873, when Mosler³⁷ suggested that bronchiectatic cavities be opened and drained. Bronchotomy, however, because of the almost uniformly bad results obtained, has been almost entirely abandoned. Mumford and Robinson,³⁸ in 1902, collected 33 cases of bronchiectasis from the literature in which a bronchotomy had been performed, with a mortality of 62 per cent. Garre³⁹ had a 37 per cent and Koerte⁴⁰ a 78.6 per cent immediate mortality, following surgical drainage in bronchiectasis. In 1911, Sauerbruch⁴ was able to collect 123 cases of bronchiectasis which had been treated by pneumonotomy.

Thirty-three per cent were cured, 5 per cent were improved, 27 per cent were unimproved and 35 per cent died. Within recent years, however, beneficial effects in isolated cases have been reported by Lilienthal,⁴¹ Ribadeau-Dumas and Mocquot.⁴² The pneumonotomy performed by Graham in his cautery pneumectomy will be discussed under lobectomy.

Sauerbruch,⁴ because of the high mortality obtained following pneumonotomy in bronchiectasis advocated the production of fibrosis of the lung by ligating the pulmonary artery. In 1911, he reported 2 cases of bronchiectasis so treated. Henschen⁶ reported the result of 7 cases operated in Sauerbruch's Clinic in this way. One patient showed extensive improvement, practically a cure. In another there was slight improvement. In 2 no change was demonstrated. In 2 others, no conclusions could be drawn, because the report was made too soon after operation. In the last case it was necessary to resort to pneumonotomy. Because of the marked shrinkage and fibrosis of the lung produced by this procedure, Henschen⁶ advised that the ligation of the pulmonary artery be followed by a thoracoplasty.

At the present time the most widely practised surgical procedure in bronchiectasis is some form of surgical collapse. Mumford and Robinson,³⁸ in 1912, advocated the production of an artificial pneumothorax in those cases of bronchiectasis in which there were no adhesions between the parietal and visceral layers of pleura. McGregor⁴³ believes that an artificial pneumothorax should be used in all cases of bronchiectasis as a preliminary procedure. Artificial pneumothorax has been used recently by Duken,⁵ Brauer³¹ and Whittemore.⁴⁴ In a review of the literature by Whittemore and Balboni,⁴⁴ 93 cases of bronchiectasis were collected which had been treated with artificial pneumothorax. Fourteen were reported as cured; 44 reported as improved, this improvement varying from slight to really great improvement; 7 died, 2 of which deaths followed thoracoplasty; in 12 cases a pneumothorax could not be produced; and there was a rupture of the pleural cavity in 3. Whittemore and Balboni conclude, however, that, even though a review of the literature shows such a high percentage of cures following the production of an artificial pneumothorax, this procedure should not be considered a curative measure. They feel, however, that it may be used as a preliminary procedure, and if no lasting benefit is obtained following its use more radical surgery can always be resorted to.

The form of collapse therapy which is most frequently employed at the present time is that of thoracoplasty. Koerte,⁴⁰ in 1908, reported 3 cases of bronchiectasis in which a thoracoplasty had been performed. One of these died of brain abscess; in one the results were uncertain; and in one a cure resulted. Mumford and Robinson³⁸ in 1912, reported 3 cases in which an extensive rib resection had been

performed with two deaths and one patient barely escaping death. Sauerbruch,⁴ in 1911, reported unfavorable results following the production of a thoracoplasty in bronchiectasis. He emphasized at this time the necessity of energetic orthopedic after treatment in cases in which a thoracoplastic operation has been carried out. In 1920, he reported his results in 27 cases; 5 patients were permanently benefited, one obtained only temporary improvement, one died and one became worse after a year. In 11 cases there was definite improvement. Henschen⁶ reported 14 cases treated by thoracoplasty in Sauerbruch's Clinic. Two patients were improved to such a degree that they might be considered cured; 4 were somewhat improved, and the remaining 14 showed practically no results. There was no mortality. Hansen⁴⁵ reported 2 cases in which thoracoplasties were performed with absolutely no results. Hedblom^{15, 46} has been the American exponent of the extrapleural collapse in bronchiectasis, and has especially emphasized the value of "graded" thoracoplasty. In 1924, he reported 18 cases in which an extrapleural thoracoplasty had been performed for bronchiectasis. There was no postoperative mortality, and at the time of report there were no deaths. Following this procedure the decrease in sputum averaged from 75 to 100 per cent. In 1927, a subsequent report was made on this series of cases, all patients having been followed for three years postoperatively. Three had died, one of fatal hemoptysis, one of actinomycosis of the chest wall ten minutes after operation and the other of acute poisoning. Six had been markedly improved, the sputum ranging from an average of 60 to 90 cc. in twenty-four hours. Five had been practically cured. One of these 5 still raised from 60 to 90 cc. of sputum, whereas before operation he raised from 500 to 1000 cc. In the same year, Hedblom⁴⁶ reported the records of 9 additional patients, 2 of whom died of pneumonia following a three-stage operation. In 3 a secondary lobectomy was undertaken and in 4 the sputum was reduced from 90 to 30 cc. in twenty-four hours. Lilienthal,⁴⁷ who originally was opposed to thoracoplasty in bronchiectasis, recently has reported some very good results following this procedure. Brauer³¹ feels that thoracoplasty is the best method of collapsing the lung, as the maximum amount of collapse is thus obtained. Hedblom emphasizes that thoracoplasty should be reserved for those cases of undoubted bronchiectasis. In cases complicated by multiple and multilocular abscesses the procedure is attended with a high mortality. Considerable improvements following thoracoplasty have been reported by Edwards,⁴⁸ Duken⁵ and McGregor.⁴³ Sauerbruch,⁴ who previously performed a number of thoracoplasties, in a recent contribution concluded that thoracoplasty in bronchiectasis is of no value except in the cases of so-called "retraction bronchiectasis." He states that the failure to obtain results in the other types of bronchiectasis can be understood when one considers that the

bronchi of a bronchiectatic lung cannot be compressed even by a pressure of 80 to 100 pounds. As has been described under the heading of Pathology, bronchi, especially those of the larger diameter become markedly thickened, fibrosed, and may even become calcareous, so that relatively little collapse can be expected following these various procedures. Undoubtedly if desirable results are to be obtained, they can be obtained only in early cases in which there is relatively little change in the bronchi.

Operations on the phrenic nerve, such as division or evulsion of the nerve, have been advocated in bronchiectasis. Very striking therapeutic results have been reported by Rist,²¹ Chauffard and Ravina,⁴⁹ Brauer,³¹ McGregor,⁴³ Harrington⁵⁰ and Davies.⁵¹ Brauer³¹ advocates phrenicotomy, because it is less radical than thoracoplasty and is of especial value when the bronchiectasis is limited to the lower lobe and is not extensive. Harrington⁵⁰ advocates this operation as a preliminary operation to a more extensive collapse operation. Davies⁵¹ reported 5 cases of bronchiectasis in which a phrenico-exaeresis was performed, distinct benefit being obtained in three.

Lobectomy.—Because of the relatively poor results obtained by the drainage of bronchiectatic cavities and also attempted collapse, extirpation of the involved lobe has been performed in a large number of cases. Lenhartz⁵² first advocated lobectomy in bronchiectasis. Heidenhain⁵³ was the first to successfully remove a lobe of the lung for bronchiectasis, following which a bronchial fistula persisted, however. Since this pioneer work, the number of cases so treated has increased considerably. In 1914, Meyer⁵⁴ was able to collect 16 cases of bronchiectasis in which a lobectomy was done, with a mortality of 50 per cent. Lilienthal,⁵⁵ in 1922, was able to collect from the literature only 30 cases in which a resection of the lung had been performed for suppurative bronchiectasis. He reports 31 cases of bronchiectasis in which a lobectomy was either performed or intended. In 14 of these, in which a single lobe was removed for disease limited to that lobe, 6 died, a mortality of 42.8 per cent. In 10 cases, in which the disease was not limited to a single lobe and in which the operative procedure entailed the removal of more than a single lobe, there were 7 deaths (mortality, 70 per cent). In the remaining 7 cases a lobectomy was attempted but could not be completed, an exploration only being done. Five of these patients died, although none of them died on the operating table. All but 2 of the completed cases were cured. One patient still had productive cough and sputum which had no odor. Lilienthal,⁵⁶ five years later, reported the results obtained in 34 cases in which lobectomy was performed by him, in some cases one lobe, in others two lobes, and in still others the entire lung, was removed. There were 7 patients (20 per cent) which were perfectly well. He makes a plea for this method of treatment. Graham,⁵⁷ in 1923,

collected 45 cases of bronchiectasis from the literature in which a lobectomy had been performed. Twenty-five of this number had died, giving a total operative mortality of 52 per cent. He reported 3 cases of bronchiectasis in which a lobectomy had been performed by him. Two of the patients died following the second stage; in the third case the operation was successful and resulted in a cure. Of the 48 cases, including the 3 reported by Graham, only 8 could be considered as successes (17 per cent). Because of the high mortality obtained in cases of bronchiectasis treated by lobectomy, Graham⁵⁸ advocated cautery pneumectomy in chronic suppurative bronchitis. Subsequently he⁵⁹ reported 45 cases of various types of chronic pulmonary suppuration in which a cautery pneumectomy was performed. There was an immediate mortality of 6.6 per cent and a late mortality of 11.2 per cent within a period of three years. Sixty-nine per cent of these cases were free from symptoms. Ten of these still have bronchial fistula. Robinson⁶⁰ reported 7 cases of bronchiectasis in which lobectomy was performed, with 3 deaths. Hansen⁴⁵ reported 4 cases with one death. Recently, Brunn⁶¹ reported 6 cases in which lobectomy was performed, 5 of which were for bronchiectasis, with one death.

As a less radical procedure, Garre,⁶² in 1902, advocated bringing the diseased lobe, in bronchiectasis, outside the chest wall and suturing it to the chest wall, in order to produce a shrinking of the lung. In a case in which this procedure was performed it became necessary to open the lobe and later remove it. Whittemore³⁶ reported 5 cases in which this procedure was performed. Of these 2 were completely cured, one was improved, one developed pneumonia on the tenth day and died, and the fifth patient, who was operated upon only six weeks before the report, was making a good convalescence. In those cases of bronchiectasis in which the process is limited to a single lobe and in which the symptoms are severe enough to justify the performance of a lobectomy, the greatest amount of relief is obtained by this operation, as it permits a complete removal of the diseased process. Because, however, over half of the cases of bronchiectasis are bilateral and because of the high mortality in bronchiectasis, varying from 10 to 50 per cent, the procedure is applicable to relatively few cases.

Medical Treatment.—Ever since the condition of bronchiectasis was first described by Laennec,⁶³ the treatment has been largely medical, or conservative, even though conservative therapy has been more or less unsuccessful and unsatisfactory. The introduction of postural drainage by Quincke,⁶⁴ in 1898, was one of the most noteworthy advances made up to that time. In addition to postural drainage, which is of distinct value in all cases of chronic pulmonary suppuration, various other conservative measures have been employed in cases of bronchiectasis. Recently, Weinberger⁶⁵ has reported a case treated only by postural drainage, which treatment

resulted in a practical cure. Intratracheal injection of antiseptic fluids has been more or less unsatisfactory. The substances used have been menthol, iodoform and creosote. One can realize how ineffective the medical treatment of bronchiectasis has been only after consulting some of the standard textbooks on medicine and noting the large number of drugs which have been used in the treatment of this condition. At the present time the medical treatment of bronchiectasis consists primarily of postural drainage, the intratracheal injection of various medications, and, in certain continental clinics, dehydration. The latter, the "thirst cure," consists of reducing the intake of fluids by the patient, which results in a definite diminution in the amount of sputum. Recently Schott,¹⁰ and Guillemot and Michaux⁶⁶ have reported beneficial results obtained by the thirst cure. Vaccine therapy has been employed by Steinmeyer and Kathe¹¹ in bronchiectasis, with absolutely no changes. Whittemore³⁶ is very emphatic in condemning the medical treatment of bronchiectasis. He states, "I do not believe that irrigation of the bronchial tree or the injection of medicated oil has any bearing on curing the condition."

Since the first introduction of iodized oil into the tracheobronchial tree by Sicard and Forestier³⁴ in 1922, iodized oils, especially lipiodol, have been used in a large number of cases. The procedure has been used most extensively as a diagnostic one, but a number of the observers have observed that patients filled with iodized oil also were improved following the introduction of the oil. Such beneficial effects have been noticed by Lenk and Haslinger,³⁵ Moeller and Magnus,⁶⁷ Sgalitzer,⁶⁸ and others.⁶⁹⁻⁸² The beneficial effects obtained by repeated intrabronchial introductions of iodized oil in bronchiectasis have been mentioned in a previous publication.³³ Belfield and Rolnick⁸³ have shown that iodized oil, when injected into infected seminal vesicles, exerts a direct bactericidal effect. Recently, Ransohoff and Heiman⁸⁴ have reported 5 cases of empyema in which iodized oil used primarily as a contrast substance caused a rapid healing and closing of the thoracic wounds. In each of the 5 cases Dakin's solution had been employed, according to the technique of Carrell without any apparent results.

There is some question concerning the manner in which the oil exerts a beneficial effect in bronchiectasis. The author has found, following the intratracheal introduction of iodized oil, a progressive diminution in the number of organisms contained in the sputum. This parallels the improvement in the patient's condition clinically. Whether this is due to a bactericidal effect of the iodized oil or whether it is due to displacement of the bronchial secretions is not known. The author believes that the bactericidal action is the more important of the two.

In contrast to these beneficial results obtained following the introduction of iodized oil into the tracheobronchial tree, other

observers have been unable to obtain any therapeutic effects. Neuswanger⁸⁵ smeared agar plates with lipiodol and the following organisms: *Bacillus coli*, streptococcus, hemolyticus and *Staphylococcus aureus*. As the organisms grew well, even in close proximity to the oil, Neuswanger concluded that lipiodol was neither bactericidal nor bacteristatic. Archibald and Brown⁸⁶ mixed lipiodol with sputum. This mixture was then plated on various culture media. In each instance a profuse growth of organisms resulted. They concluded that the oil was not bactericidal. These experiments were performed *in vitro*, however, and the results obtained are not comparable to those obtained clinically. In the author's own experiments he has been able to show repeatedly that following the introduction of oil into the tracheobronchial tree the number of organisms contained within the sputum as determined by actual count per cubic centimeter decreased progressively. In a previously reported case, this decrease in a number of organisms following introduction of iodized oil is definitely shown.⁸⁷

Is the intrabronchial injection of iodized oil safe and justifiable? Before such a procedure should be performed, either as a diagnostic or a therapeutic measure, one must be convinced that the procedure is not without danger, even though the therapeutic or diagnostic effects be desirable. Since the first introduction of iodized oil into the tracheobronchial tree by "Sicard" and Forestier,³¹ in 1912, thousands of patients have been filled with iodized oil by hundreds of different observers, with few untoward results. In 1927, Pritchard, Whyte and Gordon⁷⁹ reported a series of over a thousand cases in which bronchography had been used. The author has employed bronchography, either as a diagnostic or therapeutic measure, in over 1500 instances. The greater majority of these fillings have been performed for therapeusis. In the author's series there has never been any untoward reaction. In 6 cases there was evidence of iodism, varying from a slight rhinitis to a rather severe erythematous rash. All the reactions disappeared within forty-eight hours. None of the reactions were at any time alarming. In addition to the clinical there is considerable experimental and pathological evidence of the innocuousness of the intratracheal introduction of iodized oil. Sicard and Forestier,^{34, 88} in a large series of animals, were unable to demonstrate any pathologic changes in the bronchi or lung following the introduction of lipiodol. Brauer⁸⁹ injected iodopin into the lungs of patients with advanced paralysis or carcinoma, and at autopsy found no evidence of irritation from the iodized oil. Pinkerton,⁹⁰ in determining the reaction of the lung to various oils and fats, found that the iodized oils which are used clinically produce practically no reaction in the lungs of animals in contrast to animal oils, which cause an intense pulmonary reaction. Sullivan, Friedbacher and McKinley⁹¹ administered repeated

doses of iodized oil intrabronchially to dogs over long periods of time. The amount of oil employed was relatively greater than the amounts used to fill human beings, as the average dose given to a dog at each filling was 10 cc. The number of fillings varied from 4 to 9. At autopsy, no gross change was demonstrable. Microscopically, there was "in some cases a small amount of fibrosis and, in occasional areas toward the periphery, was chronic passive congestion." Fried and Whitaker,⁹² working with cats, introduced iodized oil in amounts varying from 1 to 10 cc. They found that if the oil did not exceed 3 or 4 cc. the animal was not disturbed. In no instances, even in those animals receiving large doses of the oil, was there any evidence of inflammatory change in the lung, but doses exceeding 1.5 cc. of the oil per kilogram body weight was not well tolerated by the animal. Peiper and Klose,⁹³ on the other hand, conclude, from their experimental work with animals, that the introduction of iodized oil into the trachea is dangerous, as they were able to produce very severe changes in the lungs of rabbits following the introduction of 20 cc. of oil. That their results can be disregarded is self-evident, because of the exceedingly large amounts of oil given to such relatively small animals, the doses being distinctly out of proportion to that given to the human being. Sicard and Forestier,⁹⁴ in over 5000 intratracheal injections of iodized oil, observed no untoward effects.

Severe iodine reactions have been reported by Belote⁹⁵ and O'Donovan.⁹⁶ Miller and Eglee⁹⁷ observed 2 cases of iodism, one of which consisted of a very acute toxic erythemia associated with generalized edema. Blumberg⁹⁸ advises against the use of iodized oil in cases of hyperthyroidism, kidney or heart lesions and patients inclined to iodism. Deleterious effects following the use of iodized oil in cases of pulmonary tuberculosis have been reported by Aumonte, Leurat, Secousse and Caussimon,⁹⁹ Archibald and Brown,⁸⁶ Lichtwitz¹⁰⁰ and Ballou.¹⁰¹ The author agrees with the above observers that iodized oil should be used very cautiously in pulmonary tuberculosis, especially in parenchymatous variety. He has had good results in the fibroid type of tuberculosis, in which the patient is suffering more from the secondary infection of his cavities than from the tuberculous process. Such a case is reported in a previous publication.⁸⁷

As has been stated previously, in the author's series of cases no untoward reactions have been observed, aside from the 6 instances of iodism. In this series of 1500 bronchographies, 112 cases of bronchiectasis were treated by repeated introductions of iodized oil into the tracheobronchial tree. The largest number of fillings received by any one patient was sixteen. The diagnosis of bronchiectasis was made in each case by the fluoroscopic observation of the mode of filling of the bronchi. Roentgenograms were made for confirmation and record. That the fluoroscopic observation of the lung during the filling of the alveoli and the observation of

the mode of filling of the bronchi is more important than the interpretation of the radiographic plate has been stressed elsewhere.^{33, 87, 102} In the cases so treated a definite improvement was noted in each one. In 35 cases (32 per cent), there was complete relief of all symptoms, yielding a symptomatic cure, even though there still remained radiographic evidence of bronchial dilatation. In 4 cases not only was symptomatic relief obtained, but also the dilatation of the bronchi, as determined radiographically disappeared. In these cases undoubtedly there was no organic change in the wall of the bronchi but merely a functional dilatation of the bronchi which disappeared following the control of the infection. In the remaining patients, the improvement was so marked that none of the patients cared to interrupt the treatment. In 41 cases (36 per cent) symptomatic relief was obtained, but following an acute respiratory infection there was a return of some cough with a slight amount of sputum. This was, however, never as severe as before the introduction of iodized oil. These symptoms responded quickly to one or two subsequent treatments. In the remaining 36 (32 per cent), improvement was marked. The patients are still under treatment, and still have some cough or sputum or both. Invariably the improvement was evidenced by a decrease in the amount of sputum, a disappearance of the odor of the sputum, if such had been present, an increase in the appetite, and a definite increase in weight, often amounting to as much as 20 to 50 pounds. Any fever which had been present disappeared, and the patient presented an entirely different appearance.

From these results it can be seen that distinct benefit can be obtained in bronchiectasis from repeated intrabronchial injections of iodized oil. The author does not feel that iodized oil is a panacea for all cases of bronchiectasis, but those cases in which there is relatively little pathology or a bilateral process, as well as other cases in which a surgical procedure is not indicated, may be greatly benefited and possibly even cured by the repeated introductions of iodized oil.

It is still too early to say what the ultimate result will be in these cases. Whether the dilated bronchi and cavities will become filled with granulation tissue, and later fibrose, is still unknown. The fact that the patient can be symptomatically cured after a series of from 1 to 10 injections makes it seem advisable to attempt the procedure in all cases of bronchiectasis before resorting to surgery. If the introduction of the oil can be performed in a way which is not difficult for the physician nor unpleasant to the patient, one is justified in employing it in all cases of bronchiectasis, even the earliest, where, undoubtedly, the conservative therapy offers the most. The method which the author has used in his entire series is the "passive" technique, which has been described in detail in previous

publications.^{33, 87, 102} Briefly, it consists of anesthetizing the anterior pillars of the pharynx, which abolishes the swallowing reflex. Because of the abolition of the swallowing reflex, swallowing is impossible, and the larynx, which normally rises during deglutition to lie beneath the epiglottis and the base of the tongue, remains immovable. The iodized oil taken into the mouth is then aspirated into the trachea and bronchi. The "passive" technique has definite advantages over the other techniques. It is extremely easy to perform; it permits of the fluoroscopic observation of the mode of filling of the bronchi, and is not at all unpleasant for the patient. In the entire series of patients so treated, no patient ever objected to a refill. It is self-evident that if complicated and cumbersome methods are to be employed, bronchography will be performed in relatively few cases, thereby precluding its use as a therapeutic measure in most cases, as well as a diagnostic procedure in the early cases of bronchiectasis giving a rather atypical history—the patient with "chronic bronchitis."

Conclusions.—1. Bronchiectasis is one of the, if not the, most frequent chronic pulmonary affections.

2. The etiology of bronchiectasis is varied. Chronic bronchitis, influenza, and nasal sinusitis are the most frequent causative agents.

3. About 90 per cent of a series of individuals suffering from chronic bronchitis and recurring attacks of acute bronchitis showed evidence of bronchial dilatation.

4. The symptoms and signs of bronchiectasis as described in textbooks represent a late stage of the condition.

5. The Roentgen ray visualization of the tracheobronchial tree following the intratracheal introduction of iodized oil permits the early diagnosis in bronchiectasis.

6. Bronchiectasis limited to a single lobe is ideally treated by extirpation of the involved lobe. Because of the frequent bilateral involvement and the high mortality resulting from such a procedure, relatively few cases can be treated. The cautery pneumectomy of Graham is the method of choice.

7. The medical or conservative therapy in bronchiectasis has been unsatisfactory heretofore. Postural drainage is, however, of distinct benefit.

8. The repeated intratracheal introduction of iodized oil in cases of bronchiectasis is of distinct therapeutic value. The results of 1500 bronchographies are reported. One hundred and twelve cases of bronchiectasis were treated. Thirty-two per cent were symptomatically cured; 12 per cent of the number showed radiographic evidence of cure. Thirty-six per cent obtained symptomatic relief, but following an acute respiratory infection had a temporary relapse. Thirty-two per cent were improved, and are still under treatment.

9. The "passive" method of introducing the iodized oil is the method of choice because of its simplicity and ease of performance.

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ABSCESS OF THE LUNG: A BACTERIOLOGIC STUDY BASED ON ONE HUNDRED AND EIGHTEEN CASES.

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MANY excellent studies on the etiology of abscess of the lung are recorded in medical literature. A number of them are concerned with the mechanism of transportation of the infectious agent to the lung. Hartwell¹ in 1920, Lambert and Miller² in 1924 and Ermatinger³ in 1928 have reported on cultures taken from the pus of pulmonary abscess cases. The last paper cited is chiefly concerned with this particular phase of the subject.

This article presents a bacteriologic study of the pus collected directly from the bronchus of 118 cases of pulmonary abscess, by means of the bronchoscope. I believe that cultures so obtained, more nearly represent the true bacterial flora present in these lesions than do those made from washed sputums. Cultures made at postmortem are hardly representative, for reasons tersely expressed by Hasslinger and Sternberg.⁴ This method is perhaps inferior to that of taking cultures from the abscess cavity directly, at open operation. However, this is not often feasible. In this series of cases about 25 per cent were referred to the surgeon for external drainage. Whenever the opportunity presented itself to take cultures at open operation and the interval between the last culture made from bronchoscopically collected pus and the surgical operation was not too great, such cultures were made. There was practical but not absolute agreement between the two sorts of cultures.

The Clinical Material. The material was obtained from the Chevalier Jackson Bronchoscopic Clinic and from Dr. John B. Flick, of the Service of Dr. John H. Gibbon, Jefferson Hospital. The pulmonary abscesses from which pus was collected for bacteriologic examination, represented both acute and chronic lesions. Most of the patients were in the third and fourth decade. The youngest patient was three and a half years of age, and the oldest was sixty-three years. The abscesses followed tonsillectomy, 40; extraction of teeth, 9; surgical operation other than those enumerated, 12; acute respiratory infections, 16; pneumonia, 17; pleurisy, 1, and of questionable origin, 23.

Technique. The material was collected by the bronchoscopist in the following manner: The larynx was exposed by means of a laryngoscope and a bronchoscope was then introduced through it into the tracheobronchial tree. An aspirator which could reach into the bronchus was passed through the bronchoscope and the pus aspirated directly, from the area of infection. Certain observations were made to determine whether bacteria were carried down into the tracheobronchial tree from the pharynx during the introduction

of the instrument. This has been discussed in a previous paper.⁵ When the opportunity afforded itself, cultures were taken from the pus of the abscess cavity at surgical operation.

Smears of the bronchial pus were made and stained by Gram's method (Burke's modification) and examined microscopically. Then a portion of the pus was inoculated into a 1 per cent dextrose hormone broth and another portion, plated upon human blood, agar plates. The titer of the media used, ranged between pH 7.6 and pH 7.8. The cultures were incubated at 37.5° C., and examined at the end of forty-eight and seventy-two hours and appropriate transplants were made. Such cultural, biologic and serologic methods deemed necessary, were employed to identify the organisms. Certain organisms were inoculated into animals. When pneumococcus was suspected in the smears, a mouse was inoculated.

Every specimen of pus was subjected to dark-field examination. This was especially intended to disclose the presence and morphologic characteristics of the spirochetes. Fontana's stain and certain of the aniline dyes were also employed for this purpose. In the early cases studied, no systematic attempt was made to culture anaërobes, but lately a portion of pus has been routinely inoculated into deep tubes of glucose (1 per cent) cysteine hydrochlorid (0.1 per cent) agar previously heated to expel oxygen. These were sealed with equal parts, by weight, of paraffin and white vaseline. They were incubated from three to five days at 37.5° C. At the end of this time, the tubes were fractured, by applying a hot rod to a circumferential file mark etched on the tube. Colonies were picked and transferred as the necessity for further study arose.

Results. The accompanying table exhibits the kind of bacteria and the number of times each organism was isolated from the lungs

INCIDENCE OF BACTERIA IN PUS FROM LUNG ABSCESES ASPIRATED
BRONCHOSCOPICALLY.

Streptococcus	{ Hemolyticus 34 Viridans 44 Nonhemolyticus 15 }	93
Micrococcus catarrhalis	61
Pneumococcus	50
Bacillus influenzae	41
Staphylococcus albus	39
Staphylococcus aureus	22
Diphtheroid bacilli	29
Spirochetes	25
Fusiform bacilli	25
Micrococcus tetragenus	22
Micrococcus pharyngis siccus	9
Friedländer group	6
Bacillus pyocyaneus	2
Diplococcus flavus	4
Bacillus proteus	2
Bacillus bronchisepticus	2
Bacillus coli communis	1
Yeasts	1
Unidentified	17
Total	451

of abscess cases. Of the 118 cases of pulmonary abscess, 20 were studied by anaërobic methods. Anaërobic streptococci were obtained in 14 of the cultures and *Staphylococcus parvulus*, in 8 of them. Fifteen other anaërobic organisms were obtained. They were chiefly rods; some were fusiform in character and a few had the morphologic characteristics of the spirilla. All cases of tuberculosis have been excluded. In this report the diphtheroid bacilli and the Friedländer group of organisms are reported as groups rather than as individual organisms. In the individual case usually more than one organism was isolated and occasionally 7 or 8 were recovered.

Comment on Individual Organisms. In this series of cases of pulmonary abscess, the streptococci (79 per cent) were of the most frequent occurrence. Of these the viridans type was present most often and nonhemolytic streptococcus was the most infrequent. The abscesses from which hemolytic streptococci were isolated were usually acute and practically all of these patients were very ill. Anaërobic streptococci were the commonest of the strictly anaërobic microorganisms recovered from cultures made by such methods. A microorganism somewhat allied to the streptococcus, the pneumococcus, was present in 42 per cent of the cases. A large percentage of these organisms were typed and the majority of them were Type IV pneumococcus. Type I pneumococcus did not occur in this series.

Both Ermatinger³ and Hartwell¹ have called attention to the frequency and importance of *Staphylococcus aureus* in the pus of pulmonary abscess cases. In my series of cultures it occurred in 19 per cent of the cases. *Staphylococcus albus* (31 per cent) had a much higher rate of occurrence than the former bacterium. Many of the aureus type of staphylococci were hemolytic when grown on blood plates. Like the hemolytic streptococci they produced acute lesions and were associated with severe systemic reactions. From anaërobic cultures a minute, gram negative staphylococcus was isolated on eight occasions. This organism morphologically and culturally conformed to the description of *Staphylococcus parvulus* of Veillon and Zuber.⁶

The frequency of *Bacillus influenzae* (34 per cent) is of interest chiefly because of the many controversies this organism has engendered with regard to its rôle as the etiologic factor of influenza. Certainly, in this instance it was often isolated from patients who gave no history of having had that disease. Yet when one carefully observed blood plates heavily peppered with influenza colonies, and few other organisms, there arose a strong presumption that this organism has very definite pathogenic properties.

Fusiform bacilli and spirochetes were encountered in 22 per cent of the cases. The organisms were identified for the most part by their morphology and motility in the dark-field examination and by smears stained by Fontana's method or with Sterling's aniline gentian violet. I consider aniline gentian violet by far the best aniline

dye with which to study the morphologic detail of these organisms. It stains intensely, so that granules, particularly those in the fusiform bacilli, are well demonstrated.

The spirochetes studied exhibited two types of motility, a lashing type and a boring or corkscrew motility. The organisms varied in length, thickness and in the number of their spirals and in the amplitude and depth of their spirals. Cultures (Noguchi⁷) were made to recover the spirochetes. The results were variable and fraught with many failures. However, on a few occasions impure cultures were obtained. Their outstanding character was the extremely fetid odor which they produced.

I concur with those who believe that the spirochetes found in pulmonary abscess are not of a single kind and that most likely they represent a variety of organisms more or less closely allied. It is worthy of comment that a few of these fusilospirochetal cases had no hematemesis; the sputum was not particularly foul and the patients were not exceedingly ill. Then another peculiarity between the finding of spirochetes and the history of the abscess, is the fact that occasionally a pulmonary abscess followed a surgical operation in a remote part of the body. For example, spirochetes were recovered from a lung abscess which followed a prostatectomy performed under general anesthesia.

Bacillus pyocyaneus was recovered in two instances; once in an abscess following pneumonia and again in an abscess following an osteomyelitis of the jaw bone. On two occasions organisms resembling *Bacillus bronchisepticus* in all respects, were isolated. These organisms have been reported by Walker⁸ in human lesions of the upper respiratory tract. Various other aërobic and anaërobic microorganisms are listed. Most of them seem to warrant no special comment. Among the anaërobic bacteria there were numerous rod-shaped organisms, some had branching forms, others clubbed forms and still others contained granules. They grew very slowly. Some are still under investigation and others were not identified. They included a few cocci and rods.

Discussion. If one scans the table of bacteria isolated in this group of cases, one is impressed with the marked similarity between these microorganisms and those common to the mouth and upper respiratory tract. It is not the purpose of this paper to enter upon a discussion of the mechanism by which pulmonary abscess is produced but it seems justifiable to conclude that if aspiration of mouth bacteria be not the cause of abscess of the lung, the bacteria are at least the potential source of further infection. This point is important and ought not to be neglected in any consideration of the etiology and development of pulmonary abscess.

Since most abscess cavities are infected with a variety of bacteria it is hardly fair to assume that any one of them is the etiologic factor. The mere presence of an organism in an abscess cavity, even though it be a virulent one, is insufficient evidence for ascribing to it a

causative rôle. That the organisms are for the most part pyogenic in nature and contribute to the underlying cause, be it tissue damage from infarction or infection, there seems little doubt. It is admitted too, that among the many organisms present, one or more may be the exciting cause.

In some instances this study furnished me with an opportunity to take repeated cultures on the same individual, over periods of weeks and months. There were almost constant changes in the bacterial flora. It is true that such changes were not marked in character but nevertheless they represent some alteration in the microbic content of the pus. To illustrate the observation, the findings are recorded in a few cases. The original cultures of J. J. contained *Streptococcus hemolyticus*, *Diplococcus pneumoniae*, *Staphylococcus albus*, *Diphtheroid bacilli*, *spirochetes* and *fusiform bacilli*. A month later *Micrococcus catarrhalis* was found, but the diphtheroid organisms were no longer present in cultures. M. K. had pus removed bronchoscopically on November 3, 1928. The cultures contained *Streptococcus viridans*, *Micrococcus catarrhalis*, *Bacillus influenzae* and a Gram negative, nonmotile rod, which produce an opaque glistening abundant chrome yellow growth on potato. On March 28, 1929, pus from the same patient when cultured yielded *Staphylococcus albus*, *Micrococcus tetragenus*, *Streptococcus viridans* and a *Diphtheroid bacillus*. H. C. who had an abscess, had on September 24, 1928, in cultures seeded from aspirated pus, *Streptococcus viridans*, *Bacillus influenzae* and a *Diphtheroid bacillus*. Cultures made on October 18, 1928, contained *Streptococcus viridans*, *Bacillus influenzae* and *Micrococcus catarrhalis* and a further bacteriologic study on November 8, 1928, disclosed the *pneumococcus*, *Bacillus influenzae*, *Streptococcus nonhemolyticus* and *Micrococcus catarrhalis*.

One might raise certain objections here. It might be assumed that the organisms not found on a first or second culture were so few, that they failed to grow or others were so numerous, that they were inhibited from growing. Such a condition is possible but then one cannot lose sight of the fact that if this be the case, the numerical disproportion between the several organisms very likely existed in the abscess cavity. I believe that such changes in bacterial flora further substantiate the points already made.

Further evidence is lent by the presence of *fusiform bacilli* and *spirochetes* in some of these cases. With the exception of the lesions they produce in the preputial sac and the vagina, which consideration can be dismissed in this instance, the common habitat of these organisms is in the mouth, about teeth and in tonsillar crypts. When such an infection takes place in the lung, it is fair to assume for both anatomic and bacteriologic reasons, that the infection came from the mouth. If we have an abscess following a prostatectomy, which was performed under general anesthesia, there is no further room for doubt as to how these organisms gained entrance into the

lung. For here we have an instance of infection with microorganisms whose common habitat is the mouth, following an operation in a region, the prostate, remote from the lung. But perhaps one case is insufficient upon which to base an argument. Two more of like nature occurred in this series. One abscess followed drainage of a gall bladder and another followed a forceps delivery. Both were performed under general anesthesia and both were spirochetal abscesses.

Summary. Pus from 118 pulmonary abscesses was studied bacteriologically. Streptococci were most commonly found in these cultures. Staphylococci, pneumococci, *Bacillus influenzae*, Fusiform bacilli, spirochetes, various anaërobes and other organisms, some unidentified, were also recovered. It is concluded that the organisms found in pulmonary abscess are similar, for the most part, to those found normally in the mouth and upper respiratory tract. It is not possible, ordinarily, to pick out any one organism as the etiologic factor, but it is believed that many of the organisms found in the abscess cavity gained entrance from the mouth and upper respiratory tract through the air passages.

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PARATYPHOID-ENTERITIDIS MENINGITIS.

REPORT OF AN ADDITIONAL CASE DUE TO *BACILLUS ENTERITIDIS*.

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AND

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THE following is a report of a case of meningitis due to a *Bacillus enteritidis*, which report is preceded by an analysis of the literature on the subject.

There are numerous reports on record of the finding of bacilli of the paratyphoid group in the cerebrospinal fluid. In fifteen of these cases the organisms may be accepted as members of that group. We have accepted only cases in which identification was based on indisputable cultural or serologic evidence.

The distribution of cases was as follows: Germany, 4; Italy, 3; Austria, 2; British Isles, 2; France, 2; Syria, 1; and the United States, 1. The only case in the United States previous to the one here reported was also in Philadelphia.

The ages of the patients varied from eleven days to twenty-five years and could be divided into three age groups: a year or less, 8 cases; six to eleven years, 4 cases; twenty to twenty-five years, 3 cases. In 2 cases the age was not given.

The cerebrospinal fluid was purulent in 10 instances, clear in 4, and in 1 the nature was not reported. In our case the turbidity was largely due to bacilli. This may have been true also in some of the cases reported as purulent in which the cells were not actually counted.

Blood cultures were positive in all cases in which they were made, with the exception of the case here reported.

The duration of meningeal symptoms in the fatal cases varied from one day to fifteen days, most of the deaths occurring within the first week. The disease was fatal in all cases in children under one year of age.

All of the 8 cases which came to autopsy showed purulent meningitis, 5 had enteritis, and 1 had pyelitis. Table I gives the significant data in these cases.

Report of an Additional Case. P. K., a female, aged twelve months, colored, was admitted to the service of Dr. J. C. Gittings, in the hospital of the University of Pennsylvania, on July 22, 1927, in a convulsion. According to the child's mother, it had had a normal birth and had never been ill, except for a slight cold the preceding winter. She had never had any gastrointestinal disturbance.

While playing in the street on the morning of the onset of her illness she seemed perfectly well, and shortly after 11 A.M. she fell into a normal sleep, from which she awakened at 6.15 P.M. with a sudden cry, and developed a clonic convulsion of the left upper and lower limb, which later became generalized. The convulsions persisted almost continuously until her death at 5 P.M. on July 23, twenty-three hours after the onset of the symptoms.

On admission, her weight was $19\frac{1}{2}$ pounds; temperature, 103° (axillary); pulse, 160; respirations, 40.

The convulsions started usually in the left limbs, and from there spread to include all the extremities and the face. The eyes presented a rapid lateral nystagmus during the convulsions, but were quiet and in the normal position during the intervals. The seizures were almost continuous, and were controlled only by chloroform anesthesia.

The head was moderately retracted, the parietal bosses large and the fontanelles open. There was no hyperemia nor bulging of the ear drums. The heart and lungs were clear and the abdomen showed only moderate

TABLE I.

Reported by.	Age of patient.	Spinal fluid, character.	Spinal fluid culture.	Blood culture.	Duration of life after meningitis symptoms.	Autopsy.†
Arts and Boese . . .	5 mos.	Purulent; polys. and lymphs.	B. para B or B. enteritidis Unidentified	Not done	24 hrs. ?	Purulent meningitis; internal hydrocephalus; catarrhal enteritis.
	7 wks.	Purulent		+	4 days	Purulent meningitis; internal hydrocephalus; acute gastroenteritis.
Symmers and Wilson .	4 mos.	Purulent	B. para B or B. enteritidis	Not done	?	Purulent meningitis.
Eckert	8 mos.	Purulent	B. para A	+	6 days	Purulent meningitis; enteritis nodularis.
Tolmer and Weisenbach	25 yrs.	Purulent; polys. predominate	B. para A	Not done	2 days	Purulent meningitis; enteritis.
Walterhofer	20 yrs.	?	B. para B	+	Recovery	
Hundeshagen	3 mos.	Purulent; polys. predominate	B. para B	Not done	12 days	Purulent meningitis, purulent pyelitis.
Lesne	25 yrs.	Purulent fluid	B. para B	+	Recovery	
Smith and Aberd . .	5 wks.	Turbid fluid; 90% polys.	B. enteritidis	+	7 days	Purulent meningitis; enteritis.
Caronia and Auricchio .	9 yrs.	Clear	B. para A*	+	Recovery	
	6 yrs.	Clear	B. para B*	+	Recovery	
Voight	11 days	Many polys.	B. para B	+	4 days	Purulent meningitis.
Brahdy	13 mos.	8000 w. b. c.; polys. predom.	B. para A	Not done	5 days	None.
Stuart and Krikorian .	11 yrs.	Clear fluid; few lymphs.	B. enteritidis	Not done	14 days	None.
Pansini	9 yrs.	Increased pressure; 7 to 8 lymphs. per high-power field	B. para A	Not done	15 days	None.
Lynch and Shelburne .	12 mos.	140 cells, 80% polys., myriads or organisms	B. enteritidis	Negative postmortem	23 hrs.	Nore.

* Organisms discovered during routine spinal fluid examinations in case of enteric fever.

† Only positive findings recorded. Special attention was paid to evidences of pathology of the spleen and intestines.

distention. There was no Kernig, Babinski or Brudzinski sign, but all the normal reflexes were increased.

The urine examination was entirely negative. The blood count showed: Red blood cells, 4,160,000; white blood cells, 6100; neutrophils, 57 per cent; lymphocytes, 41 per cent; large mononuclears, 2 per cent. The blood Wassermann reaction was negative.

Lumbar puncture on admission revealed a clear fluid with 140 cells, of which 80 per cent were neutrophils and 20 per cent lymphocytes. After fifteen hours another lumbar puncture showed a ground-glass appearance of the fluid with no change in the cell count, the turbidity being caused by myriads of organisms, which were easily detected in the counting chamber. As the nature of the process was still in doubt at this time, 15 cc. of anti-meningococcus serum were administered intraspinally, with no relief of symptoms.

Necropsy was refused, but a postmortem pericardial puncture revealed an entirely unsuspected large collection of serosanguinous fluid, which on culture proved to be sterile. Culture of heart's blood was also sterile.

Cultural Studies. The cultures of the cerebrospinal fluid gave a luxuriant growth of bacilli with the characteristics of *B. enteritidis*.

Morphology. An actively motile Gram-negative rod, averaging about 1 to 3.5 mikra by 0.4 mikra, and staining readily with aniline dyes. There is no spore formation.

Cultures. The organism grows readily on ordinary culture media. Agar surface colonies are delicate gray, translucent, finely granular colonies, about 1 to 2 mm. in diameter, entire, smooth, convex and having thin margins. Deep colonies are smaller and tend to be lanceolate. The growth on agar slants is abundant, reaching its maximum in forty-eight hours. The consistency is butyrous. Gelatin is not liquefied, but there is abundant growth along the line of inoculation as well as on the surface. Broth gives a heavy turbidity with a pellicle forming on the third to the eighth day, at which time a heavy granular sediment appears. On Löffler's blood serum the surface growth is abundant and cream-colored, with no digestion of the media. On potato there is a yellowish, nonspreading surface growth. Litmus milk is acidified in twenty-four hours, becoming alkaline in three or four days. There is no coagulation. Proteolysis starts in about seventy-two hours, and is almost complete in ten days. There is no hemolysis on blood-agar plates. Nitrates are reduced to nitrites. No indol is formed in peptone media. Hydrogen sulphid is produced. Acid and gas are formed in the following 1 per cent carbohydrate broths: dextrose, levulose, arabinose, inosite, dulcitate, rhamnose, mannose, mannite, zylose, maltose and galactose. There is no fermentation of inulin, dextrin, raffinose, lactose, salicin nor saccharose.

Thermal Death Point. Salt solution suspensions of twenty-four-hour agar-slant cultures were killed by heating at 55° C. for thirty minutes.

Pathogenicity. Rabbits were infected by intravenous injection of 0.5 cc. of a twenty-four-hour broth culture, and the organisms were

recovered from the intestine at autopsy. There was no evidence of meningitis in the rabbit, and meningeal cultures were negative. Subconjunctival inoculation of a rabbit produced an abscess, which cleared up in three weeks. There was no evidence of meningitis in this animal.

The cultural and biologic characteristics of this organism place it in the paratyphoid-enteritidis group. The members of this group from which it cannot be differentiated by cultural methods alone are *B. paratyphosus* B, *B. enteritidis*, *B. suipestifer* and *B. aertrycke* (de Nobile).

Serologic Studies. Agglutination tests were performed between the organism here reported, No. 20249, and the following known strains:

B. paratyphosus A, Mear's strain, originally from the Hygienic Laboratory.

B. paratyphosus B, Cool's strain, originally from the Hygienic Laboratory.

B. aertrycke, de Nobile, No. 633 American Type Culture Collection.

B. suipestifer, No. 214, American Type Culture Collection.

B. enteritidis, No. 210, American Type Culture Collection.

The tests included, first, the reaction between the unknown organism No. 20249, and sera specific for the various members of the group; second, the reaction between the various members of the group and a serum specific for No. 20249; third, the reaction of certain members of the group and the specific 20249 serum, after absorption of agglutinins from the latter by the various organisms tested.

Technique. The agglutinating sera for *B. paratyphosus* A and B were obtained from the laboratories of H. K. Mulford Company. The other antisera were prepared by the injection of killed cultures of the homologous organisms into rabbits. These antigens were salt solution suspensions of twenty-four-hour agar-slant cultures, killed by heating for thirty minutes at 60° C. The antigens for agglutination were prepared by growing the organisms for four days in nutrient bouillon with daily subculture, after which they were centrifuged at high speed for ten minutes. The supernatant fluid was then pipetted off, and the organisms were suspended in salt solution. These living antigens were used for the agglutination tests. After the agglutination tests had been set up they were incubated for two hours at 55° C. in the water bath. Readings were made at the end of this time, and again after eighteen hours in the ice box.

The technique for the agglutinin absorption tests was as follows: twenty-four-hour cultures on agar slants, after three daily subcultures, were stirred directly into 3 cc. of the immune serum to be tested, until a suspension of a standard density was obtained. The suspension was then incubated at 37° C. for two hours, centrifuga-

lized, and the clear, supernatant fluid was pipetted off and diluted as shown in the table. The balance of the test was the same as that with unabsorbed serum.

TABLE II.—AGGLUTINATION TESTS.

Immune serum.	Antigen.	Dilution of immune serum.								
		1 in 20.	40.	80.	160.	320.	640.	1280.	2560.	5120
20249*	20249	+++	+++	+++	+++	++	++	++	0	0
	B. enteritidis	+++	+++	++	++	+	0	0	0	0
	B. ærtrycke	++	++	++	+	0	0	0	0	0
	B. suipestifer	+	0	0	0	0	0	0	0	0
B. enteritidis	B. enteritidis	+++	+++	+++	+++	++	++	+	0	0
	20249	+++	+++	++	+	+	+	0	0	0
B. ærtrycke	B. ærtrycke	+++	+++	+++	+++	++	++	0	0	0
	20249	+++	+++	++	++	+	+	+	0	0
B. suipestifer	B. suipestifer	+++	+++	++	++	++	+	0	0	0
	20249	0	0	0	0	0	0	0	0	0
B. paratyphosus A	B. para A	+++	+++	+++	+++	++	++	+	0	0
	20249	++	0	0	0	0	0	0	0	0
B. paratyphosus B	B. para B	+++	+++	+++	+++	++	++	+	0	0
	20249	++	++	+	0	0	0	0	0	0

* 20249 is the organism isolated from the cerebrospinal fluid of the case here reported.

Results of Agglutination Tests. Table II gives the agglutination reactions of sera of animals immunized against the organisms in the first column, and tested with the organisms in the second. Our culture No. 20249 is agglutinated by antienteritidis serum, anti-ærtrycke serum and antiparatyphosus B serum. 20249-Antiserum agglutinates B. ærtrycke and B. enteritidis.

TABLE III.—AGGLUTININ ABSORPTION TESTS WITH IMMUNE SERUM OF B. PARATYPHOSUS B ABSORBED BY ANTIGENS NO. 20249 AND B. PARATYPHOSUS B.

Absorbing antigen.	Antigen.	Dilution of immune serum.						
		1 in 20.	40.	80.	160.	320.	640.	1280.
B. paratyphosus B	B. paratyphosus B	0	0	0	0	0	0	0
	20249	0	0	0	0	0	0	0
20249	20249	0	0	0	0	0	0	0
	B. paratyphosus B	+++	+++	+++	+++	+++	++	+

Table III shows the results of an absorption test performed to exclude the identity of No. 20249 and B. paratyphosus B., the commonest of the three test organisms mentioned above. This test reveals the fact that B. paratyphosus B could absorb all antibody from antiparatyphosus B serum, while No. 20249 could only absorb its own nonspecific agglutinin from that serum. It, therefore, did not disturb the titer of the serum for its own specific organism. This shows that No. 20249 is not B. paratyphosus B.

TABLE IV.—AGGLUTININ ABSORPTION TEST WITH IMMUNE SERUM OF NO. 20249 ABSORBED BY ANTIGENS OF OTHER STRAINS.

Absorbing antigen.	Antigen.	Dilution of immune serum.								
		1 in 20.	40.	80.	160.	320.	640.	1280.	2560.	5120.
20249	20249	0	0	0	0	0	0	0	0	0
	B. enteritidis	+	0	0	0	0	0	0	0	0
	B. ærtrycke	+	0	0	0	0	0	0	0	0
B. enteritidis . .	B. enteritidis	0	0	0	0	0	0	0	0	0
	20249	+	+	+	0	0	0	0	0	0
	B. ærtrycke	0	0	0	0	0	0	0	0	0
B. ærtrycke . . .	B. ærtrycke	0	0	0	0	0	0	0	0	0
	20249	+++	+++	+++	++	++	++	0	0	0
	B. enteritidis	+++	++	++	++	++	++	+	0	0

Table IV gives the results of agglutinin absorption tests performed with No. 20249 serum treated with No. 20249, B. ærtrycke, and B. enteritidis antigen, each of the sera being tested, after absorption, with each of the three organisms.

This test shows that organism No. 20249 takes out all agglutinin from its own serum, and takes out nearly all the specific enteritidis antibody from the anti-enteritidis serum. It takes out no agglutinin from anti-ærtrycke serum. From this, with the cultural observations, we conclude that the organism here reported is identic with B. enteritidis of Gaertner.

Summary. A review of the literature reveals 15 previous cases of meningitis from which bacilli of the paratyphoid-enteritidis group were isolated, and a sixteenth case is here reported.

Most of the cases occurred in children.

All the cases aged a year or less died, including the present case.

In most of the cases the fluid was purulent, or showed a predominance of polymorphonuclear neutrophils.

In all the previously reported cases in which blood culture was made, it was positive. In our case postmortem blood culture was negative.

Conclusions. Meningitis due to bacilli of the paratyphoid-enteritidis group is a serious condition, usually fatal in the very young. It should be suspected whenever Gram-negative motile rods are found in the cerebrospinal fluid.

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REVIEWS.

LE CANCER. By GUSTAV ROUSSY, with the collaboration of ROGER LEROUX and MAURICE WOLF. Pp. 846; 280 illustrations, and many colored plates, charts and tabulations in the text. Paris: Masson & Co., 1929.

THIS very impressive volume is a second completely revised and reset edition of Volume II of the Fifth Fasciculus of the "Nouveau Traité de Médecine by Roger," Widal and Teissier.

It is a work of really magnificent appearance, though formidable in size. It is beautifully illustrated with photographs, photomicrographs and colored plates. Unfortunately, however, it is printed upon a very highly glazed paper in order that the cuts may show to best advantage, which is bad for the reader on account of the reflections of light from the pages, which tire the eyes.

It covers the entire subject of oncology—history, philosophy, etiology, morbid anatomy, histology, experimentation, statistics, treatment, tumors of the lower animals, tumors of plants, and so forth, and, in general, the treatment is quite full and satisfactory.

Some American readers may experience difficulty with the nomenclature, which is different from that to which they are accustomed.

J. McF.

ESOPHAGEAL OBSTRUCTION, ITS PATHOLOGY, DIAGNOSIS AND TREATMENT. By A. LAWRENCE ABEL, M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon to the Cancer Hospital, London; Surgeon to the Kensington General Hospital; Assistant Surgeon to the Woolwich War Memorial Hospital; Surgeon to the London Locke Hospital. Pp. 220, including full bibliography for each chapter; 132 illustrations and 2 color plates. New York: Oxford University Press, American Branch, 1929. Price, \$9.00.

THE book is unique in that the whole subject of esophageal disease is presented in relation to its most important symptom, namely, obstruction. It is well written, interesting, and apparently based on a wide surgical experience and clinical knowledge. An exhaustive bibliography appended to each chapter shows wide reference to the literature although, occasionally, an important contribution seems to have escaped the author. The anatomic, embryologic, physiologic and bacteriologic considerations in esophageal disease are

presented. General diagnosis including instrumentarium is considered. Roentgen ray and direct esophagoscopy examination are stressed as the most important and only reliable means of arriving at the correct diagnosis in esophageal disease. Medical, Roentgen ray and surgical methods of treatment of esophageal disease are presented, but from the standpoint of the American clinician many of our well established procedures are not properly evaluated, and are discarded. Esophageal constrictions due to congenital malformations, acute obstruction including foreign bodies; cardiospasm and neuropathic affections of the esophagus, and obstruction due to extrinsic pressure are given adequate consideration. Diverticulum, pharyngo-esophageal, is considered under pathology, diagnosis and treatment. Diverticulum of the esophagus proper; chronic esophagitis, including simple ulcer, simple tumor, varices, granulomata (tuberculosis, syphilis, actinomycosis), and simple strictures of the esophagus are given three chapters. Of particular interest are the four last chapters of the book devoted to cancer of the esophagus, pathology, diagnosis, palliative treatment and radical treatment. The author strongly emphasizes the fact that the only hope of curing cancer of the esophagus lies in early diagnosis, which can be made only by direct examination with the esophagoscope. In referring to the radical cure by surgical excision the author states, "Cancer of the esophagus is so fatal that in the absence of any contraindication such as metastases, or extreme emaciation radical removal should always be attempted." The book is distinctly surgical in its point of view and is a most important contribution to the literature of esophageal disease.

G. T.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW.

Edited by ESMOND R. LONG, Professor of Pathology, University of Chicago. Pp. 301; 25 illustrations. Springfield, Illinois and Baltimore, Maryland: Charles C. Thomas, 1929. Price, \$4.00.

THOSE who cherish Camac's "Epoch Making Contributions to Medicine" as an easy and tempting way of getting back to certain important original sources were delighted to hear that Long was to follow up his History of Pathology with translations of excerpts from the works of the master writers of medicine. We use the word medicine advisedly for the history of pathology in its broadest sense is so interwoven with the history of medicine that in this volume, for example, only two or three out of the thirty-six selections belong strictly in the domain of morbid anatomy. Thus the editor has quite properly included such clinicopathologic treatises as Corvisart's "Diseases of the Heart," Laennec's immortal "Traité de l'Auscultation Mediate," Bright's "Reports of Medical Cases," and so on. The chronological order has been followed and original

passages, varying from 2 to 26 pages in length, have been selected either for their intrinsic historical importance or as representative samples of "lengthy volumes which in their entirety were of unusual influence." Following Hippocrates, Celsus, Galen and Paul of Ægina, Rhazes represents the Arabic influence, and William of Saliceto the mediæval period. In the Renaissance, we have Benivieni, Fracastor and Fernel; while Severinus, Tulp, Wepfer and Sylvius share with Harvey in the seventeenth century. Lancisi, Ruysch and Astruc lead up to the great Morgagni, while Hunter, Baillie and Bichat usher in the nineteenth century. Here the great English and French pathoclinicians are liberally represented, while our own Horner, Gerhard and Gross precede the two master pathologists, Rokitansky and Virchow.

It is a rather melancholy fact for pathologists that the last contribution considered worthy of inclusion in this series was written over seventy years ago, a longer period than had elapsed between any of the previous selections back to the fifteenth century. E. K.

MINOR SURGERY. By FREDERICK CHRISTOPHER, M.D., F.A.C.S. Pp. 694; 465 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$8.00.

THE author has presented to his readers a most instructive and comprehensive treatment of true minor surgery. It has been some time since the reviewer has had the pleasure of writing a criticism which has such little adverse criticism in it. He ventures to express the opinion that this is the most thorough, instructive, up-to-date and interesting work of the sort that it has been his pleasure to read in years. The book contains a world of information most aptly imparted to one who cares to read. The story is admirably presented and each subject is covered well. Senior surgeon, assistant surgeons, interns and students all can profit by having this book at hand throughout their daily work. E. E.

VARICOSE VEINS. By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 208; 35 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, \$3.50.

IN this little volume the author has made a résumé of a most thorough investigation of the literature throughout the world and combined it with his own experience in the care and treatment of some 800 cases of varicose veins. He discusses the embryology, anatomy, etiology and pathology of this very common condition and points out the shortcomings of surgery and the advantages of the

injection treatment. This treatment is outlined in great detail, giving the drugs, technique, induration, contraindications and complications as well as the results to be expected. The book should be read by every surgeon and internist for it presents the entire subject in a most comprehensive and convincing manner.

The volume is a well appointed, nicely written and well-illustrated example of a good piece of work. E. E.

LA TERAPIA EPATICA E LE SUE APPLICAZIONI CON PARTICOLARE RIGUARDO ALL' ANEMIA PERNICIOSA. By PAOLA INTROZZI. Pp. 75. Bologna: L. Cappelli, 1929.

FOLLOWING an interesting retrospect of the use of liver in therapeutics, the author considers the various ways in which it may exert its beneficial effect in pernicious anemia. His choice—a poor one, we believe—of the antihemolytic action of the liver is apparently based on Ferrata's teaching that the embryonic megaloblast is replaced by the normal erythroblast simultaneously with the formation of liver cells! In treating pernicious anemia, he has had good results with extracts of lymph nodes and considers that the active principle is not specific to the liver, but may be found in lymph nodes, kidney, heart and voluntary muscle. E. K.

AN OUTLINE OF ENDOCRINOLOGY. By W. M. CROFTON, B.A., M.D. Second edition. Pp. 163; 53 illustrations. New York: William Wood & Co., 1929. Price, \$3.00.

REALIZING that a medical textbook is partly out of date when it first appears, in the first edition, the author left blank pages for notes at the end of the book. In the present edition instead of revision, the notes are supplied for these pages. The book is sane, reasonably up to date and contains a surprising amount of worthwhile information within its small content.

E. K.

AN INTRODUCTION TO THE STUDY OF PHYSIC. By WILLIAM HEBERDEN (1710-1801). Pp. 159; 7 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, \$2.00.

FEW are more to be envied than the keen bibliophile whom circumstances permit to give free rein to his hobby. At the moment, rare in these days, when in addition to this he is permitted to pick up some unsuspected rarity for a mere trifle, then is he indeed in his seventh heaven. In the prefatory essay of this book, Dr. Crummer, one of our most persistent and successful "nugget" discoverers,

describes how the manuscript of this hitherto unknown work of Heberden's was brought to light. And the "Introduction" is well worth reading today for its own sake. For good measure, a reprint of Heberden's "Some Account of a Disorder of the Breast" is also included, so that we have conveniently at hand the first account of that disease of physicians, *angina pectoris*. E. K.

STEPHEN HALES, D.D., F.R.S. AN EIGHTEENTH CENTURY BIOGRAPHY. By A. E. CLARK-KENNEDY, M.D., M.R.C.P., Fellow of Corpus Christi College, Cambridge, Assistant Director of the Medical Unit and Assistant Physician to the London Hospital. Pp. 256; 14 illustrations. Cambridge University Press. Sole American Agents New York: The Macmillan Company, 1929.

MOST medical men know, or should know, that Stephen Hales was the first to measure the pressure of the circulating blood and that he successfully combined a profitable religious and scientific career. How many, however, are acquainted with his studies on the growth of bone, the chemistry of respiration and the flow of sap in trees; or with his achievements in ventilation—among the earliest in preventive medicine—or with the part that he played in successfully establishing our colony of Georgia, and in bringing the Wesleys to this country? For those who would like to know more of this interesting character the story is here told in a better and more complete form than can be found elsewhere. E. K.

THE CUSTOM OF COUVADE. By WARREN R. DAWSON, F.R.S.E., Fellow of the Royal Society of Medicine, of the Society of Antiquaries of Scotland and of the Royal Anthropological Institute. Pp. 118; 1 illustration. Manchester, England: Manchester University Press, 1929. Price, 7 shillings and sixpence.

"THE word 'Couvade' is the name applied to a curious and widespread custom that was known in antiquity, and still survives in many parts of the world. According to this custom, the father of a child, at the time of its birth, takes to his bed and behaves generally as though he, and not his wife, were the mother of the infant."

Though more ethnological than strictly medical, this book is sure to interest the inquiring medical mind. Though widespread through primitive races of all ages, including the present, the reason for this curious custom has never been satisfactorily solved. In bringing together a monumental list of examples to provide material for an intelligent discussion of the significance of this interesting problem, the author has furnished a most readable and entertaining volume. E. K.

BOOKS RECEIVED.

NEW BOOKS.

- Diseases Transmitted from Animals to Man.** By THOMAS G. HULL, M.D. Pp. 350; 29 illustrations. Springfield, Ill. Charles C. Thomas, 1930. Price, \$5.50.
- Grundlagen der ätiologischen Behandlung der Nierenentzündungen.* By DR. VIKTOR KOLLERT. Pp. 161. Leipzig and Wien: Franz Deuticke, 1929. Price, M 9.
- The Cancer Process.* By J. J. M. SHAW, M.A., M.D., F.R.C.S.E. Pp. 16. Edinburgh: E. and S. Livingstone, 1930. Price, 1 shilling.
- The Story of San Michele.** By AXEL MUNTHE, M.D. Pp. 530. New York: E. P. Dutton & Co., 1929. Price, \$3.75.
- Hypertension and Nephritis.** By ARTHUR M. FISHBERG, M.D. Pp. 566; 34 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$6.50.
- Annals of the Pickett-Thomson Research Laboratory. Vol. V. The Pathogenic Streptococci, Their Role in Human and Animal Disease, Continued.** Pp. 392; 45 plates. Baltimore: The Williams & Wilkins Company, 1929.
- The Immunology of Parasitic Infections.** By WILLIAM H. TALIAFERRO, PH.D. Pp. 414; 28 illustrations. New York: The Century Company, 1929. Price, \$6.00.
- The Medical Museum, Based on a New System of Visual Teaching.** By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M. and H. Pp. 172; 44 illustrations. London: The Wellcome Foundation, Ltd., 1929.

NEW EDITIONS.

- Incompatibility in Prescriptions and How to Avoid It.** New edition revised and enlarged. By THOMAS STEPHENSON, D.Sc., PH.C., F.R.S. (EDIN.), F.C.S. Pp. 61. New York: Paul B. Hoeber, Inc., 1929. Price, \$1.50.
- Mammalian Physiology. A Course of Practical Exercises.* A new edition. By E. G. T. LIDDELL, D.M., and SIR CHARLES SHERRINGTON, O.M., M.D., D.Sc. (CANTAB.), F.R.S. Pp. 162; 50 illustrations. Oxford: Clarendon Press, 1929.
- A very valuable book for physiological classes in any country.
- The Essentials of Histology.** By SIR EDWARD SHARPEY SCHAFER, F.R.S. Professor of Physiology in the University of Edinburgh. Pp. 628; 758 illustrations. Twelfth edition. Philadelphia: Lea & Febiger, 1929. Price, \$5.00.
- The Care of the Nose, Throat and Ear.* By W. STUART-LOW, F.R.C.S. (ENG.) Pp. 88; 18 illustrations. Second edition. London: Baillière, Tindall & Cox, 1929.
- A Textbook of the Practice of Medicine.* By Various Authors. Edited by FREDERICK W. PRICE, M.D., F.R.S. (EDIN.). Pp. 1871; 112 illustrations. Third edition. Oxford University Press, 1929.
- Bacteriology for Nurses.* By HARRY W. CAREY, A.B., M.D. Pp. 282; 44 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1930. Price, \$2.25.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Nasal Spray Method of Administering Hormones of the Ovary and Pituitary Gland.—In 1922 Blumgart suggested the application of pituitrin into the nasal mucosa in order to do away with the necessity of repeated hypodermic injections in the treatment of diabetes insipidus, stating at that time that extracts of the posterior tube of the pituitary are effectively absorbed from the nasal mucosa. PRATT and SMELTZER (*Endocrinology*, 1929, 13, 320) performed experimental tests upon rats to see if the ovarian hormone is absorbed through the mucous membrane of the nose or the vagina. They found that it was definitely absorbed from these two sites, as well as from the conjunctiva. They report upon a series of patients to whom the ovarian hormone and the active principles of the posterior lobe extracts were given by the mucous membrane of the nose route, utilizing for the application of the substances a small glass nebulizer. They report that applied in this fashion in the nose, the material is completely absorbed without sign of local irritation. When local nasal abnormalities exist, it is possible to make use of the vaginal mucosa. The advantages of the nasal method of administration over hypodermic injections are too obvious to need repetition.

Exhaustion States.—There has been an increase in the exhaustion states in the past ten years. Just why this has occurred has aroused considerable discussion. DOWDEN and JOHNSON (*J. Am. Med. Assn.*, 1929, 93, 1702) write that four causes have been suggested for this well recognized increase in the loss of a sense of well-being of the present-day generation: (1) The World War and its effects; (2) the 1918 epidemic of influenza and its persistent residuum; (3) the advent of prohibition, and (4) the oversaturation of the atmosphere with carbon

monoxid from the exhausts of automobiles. They have examined 688 patients without specific underlying disease. They note that in these individuals complaining of ease of tiring that there is a reduction in the gastric acidity; that there is a lowered basal metabolism; the blood pressure is diminished; a secondary anemia is common, as is a slow pulse. After an extremely thorough examination of these run-down individuals, they conclude that the exhaustion state arises chiefly from infections of the respiratory tract and from nervous and mental strain. To cure it, the etiologic factor must be removed. Sometimes this is a comparatively simple procedure; at other times it is extremely difficult. Under any circumstance, endocrine therapy, which they recommend, would be of no value unless the etiologic factor responsible for the production of the condition is removed.

The Effect of Guanidine Compounds on Unanesthetized Dogs.—MAJOR and WEBER (*J. Lab. and Clin. Med.*, 1929, 15, 125) state that when guanidine salts are injected into the experimental animal there is an elevation of blood pressure. Certain observers have reported in unanesthetized animals that there was a fall of pressure. In order to determine this point they observed a series of dogs who were given relatively small doses of *methylguanidine sulphate* when not under the influence of an anesthetic. Blood pressure was raised very strikingly before any toxic symptoms appeared and increase in the pressure was greater in the unanesthetized animal than in the dog under ether.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Pathologic Lesions of the Gall Bladder.—BAUMGARTNER (*Surg., Gynec. and Obst.*, 1929, 49, 780) claims that there are no characteristic symptoms or clinical data to differentiate the apparently earlier types of cholecystic disease; in the later stages, however, certain characteristic data are present. The clinical features of chronic catarrhal cholecystitis and strawberry gall bladder or cholesterosis were identical. The occurrence of stones in a fairly high percentage of gall bladders showing minimal pathologic change further substantiates the theory that gall bladders may assume a normal appearance between attacks. Chronic fibrous cholecystitis showed a higher incidence of gall-stone colic, jaundice, chills and fever than the groups of chronic catarrhal cholecystitis and strawberry gall bladder. Stones were present in 89 per cent of the cases in this group. Acute and subacute cholecystitis may occur without appreciable increase in temperature or leukocytosis. Gall stones occurred in 96 per cent of the cases. The symptoms of empyemia of the gall bladder vary greatly. The chronic form usually is not accompanied by any grave manifestations. The acute form not

infrequently is fulminating in character. Stones occurred in 96 per cent of these cases also. Gangrene of the gall bladder is associated with marked clinical manifestations. There is marked tenderness and the temperature and leukocyte count are higher than in the acute forms. Stones occurred in 96 per cent. Papillomata occur more frequently than the reported frequency. The single papilloma is friable and easily overlooked. The relation between papilloma and malignancy is problematic. Adenomata always occur in the fundus. The common types of malignant lesions are carcinoma simplex, adenocarcinoma, squamous-cell epithelioma and sarcoma.

Immediate and Eventual Features of Healing in Amputated Bones.—

BARBER (*Ann. Surg.*, 1929, 90, 985) says the same successive stages in bone healing were observed which are characteristic of repair in fractures. These are in order, vascular erosion in bone end and adjacent shaft, consequent molecular disintegration of bone adjoining the site of amputation, rounding of bony stump itself, quiescence in osteoporotic shaft, closure of medullary cavity by cap of bone, which rapidly becomes condensed, restrained production or absence of osteophytes. The time element accords well with the time of appearance of the corresponding phenomena in healing fractures. The original erosion of the amputated end is already well advanced within five or six days of the surgical trauma, even before the marks of the saw cut are obliterated from the bone. Flake-like sequestra undoubtedly occur and probably separate in less than three weeks. In amputation stumps the production of callus is much more restrained than in fractures. The medullary cap is certainly developed from the endosteal and definitive callus.

Radiation in the Treatment of Rectal Cancer.—BIRKLEY (*Ann. Surg.*, 1929, 90, 1000) writes that efficacy of radiation therapy in the treatment of rectal cancer has been greatly increased by improvement in technique. Reclassification of rectal cancer from the standpoint of the degree of radiosensitivity and of malignancy has resulted in an improved treatment of this disease. Utilization of radical surgery as an adjunct to treatment by radiation therapy is often the method of choice. The effects of treatment of this disease by any single method or combination of methods are greatly enhanced when an early diagnosis has been established. Recognition of the degree of malignancy is suggested as the determining factor in the choice of surgical route, whether abdomino-perineal or perineal if surgery is indicated.

Arsphenamin Dermatitis with Gangrene.—ROBINSON (*Am. J. Syph.*, 1929, 13, 536) states that this fatal case of arsphenamin dermatitis was the result of neoarsphenamin poisoning and could probably have been avoided if the physician had stopped therapy with the onset of itching. This is the second case of this character within three weeks' time, and the author believes that it should be stressed that neoarsphenamin is sometimes attended with severe and even fatal reactions. In reviewing the literature a case complicated with dry gangrene was noted. All the fingers and two-thirds of the hands were totally mummified.

THERAPEUTICS

UNDER THE CHARGE OF

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Experiences with the Gerson Diet in Pulmonary Tuberculosis.—SCHWALM (*Klin. Wchnschr.*, 1929, 8, 1941) reports his experiences with the diet recently described and advocated by Gerson from Sauerbruch's Clinic. It was claimed that this diet not only improves but also cures patients with severe forms of tuberculosis. The author, however, observed no beneficial effect on 20 patients. The clinical and Roentgen ray examination of the lungs showed no appreciable improvement. The gain in weight was not different from that of other patients on routine diet. The blood picture and sedimentation rate was also uninfluenced.

The Treatment of Pleuritic Effusions.—HORDER (*Brit. Med. J.*, 1929, p. 605) believes that the successful handling of a case of pleuritic effusion depends on a consideration of the following factors: (1) The cause of the infection; (2) the nature of the effusion; (3) its size; (4) the stage in the disease at which the patient has arrived; (5) the associated condition of the lung; (6) the degree of illness of the patient; (7) the contribution made by the effusion, as such, to the illness. No effort should be spared in making a diagnosis as to the nature of the infection and effusion. An active and inflammatory process in the lung should, on the whole, contraindicate the removal of pleuritic effusion, for the presence of fluid is beneficial in keeping the lung at rest. Of course, the toxic and mechanical influence of the fluid should be considered with judgment. In case the *serous effusion* (tuberculous) is large or causes respiratory or cardiac embarrassment, it should be tapped at once. If no signs of absorption are present after fourteen days, it should be tapped. Too early and too frequent removal of fluid may spread or cause a flare-up of the underlying pathologic process. Too late interference may leave the lungs permanently collapsed. If there is definite evidence that the lung is diseased, the replacement of the fluid by oxygen should be considered. Because spontaneous absorption or the removal of fluid at the proper time almost always takes care of the effusion, the author believes that the problem of *auto-serotherapy* is "a matter of supererogation." In removing the fluid local anesthesia should be used effectively. The nick of the skin with a sharp scalpel before inserting the needle is advocated. Trocars with cannules are to

be avoided. If the patient feels well there is no limit to the amount to be removed. Drugs injected into the pleura are of doubtful value. After care is important and it should be conservative. In rheumatic effusions, aspiration is seldom necessary. In lymphadenoma and cancer the individual case must determine the care. In case of *purulent effusions* and empyema, the principles of treatment of serous effusions holds, but the time factor is of greater urgency. During the active stage of pneumonia, resection and incision should be postponed, and aspiration should be repeated if necessary. In a considerable number of cases this method suffices. The character of the pus is less important than the general condition of the patient in deciding the choice of treatment. If the active process in the lungs is subsiding and the general condition is satisfactory, incision, rib-resection and drainage is the preferred method. It is very doubtful if irrigation as a routine procedure is justified by results. Irrigation at the time of operation is of questionable value, and in care of pulmonary abscess it certainly should be avoided. The care of the patient should receive special attention. Fresh air, good food, sunlight and ultraviolet rays are beneficial.

"Activated" (Irradiated) Fluorescein in the Treatment of Cancer.—Encouraging results in the treatment of certain types of malignant tumors is reported by COPEMAN, COKE and GOULDESBOUGH (*Brit. Med. J.*, 1929, p. 233). A solution of 2 to 2.5 per cent (occasionally 5 per cent) sodium fluorescein containing 3 per cent sodium bicarbonate was used. Neutral solutions were found to be inactive. The sodium fluorescein had to be activated by Roentgen rays which penetrate a filter of 4 mm. of aluminium to be effective. Because of the fairly moderate penetrating ray used for excitation there was a limit to the depth of the body at which results could be obtained. The most striking cases were those of superficial growth, such as breast carcinomata, sarcomata, malignant glands, bone tumors in thin parts, etc. Apparently the more cellular the tumor the better the results. The routine treatment outlined by the authors is as follows: (1) Paint with fluorescein solution, or administer internally; (2) irradiate with an adequate dosage of Roentgen rays or radium; (3) repeat 1, 2, 3 times, at intervals of a week; (4) allow three weeks rest; (5) repeat the complete cycle, as often as considered desirable. On the seventh day in many instances retrogression of the growth may appear. Progress seems to vary much. Four to six months continuous treatment is necessary before the result can be judged definitely. Large fungating tumors may break down so rapidly as to cause serious toxic effects. Seventy cases of malignant disease ("for the most part stated to be 'inoperable' ") were treated. Eight of the patients apparently recovered, 20 were much improved, 7 are too recent for statement; the others either showed no improvement or died. The most satisfactory response was observed in cases that had not been treated by any method previously. In superficial secondary growth, injection of the tumor with a few drops of fluorescein solution often resulted in rapid disappearance of the growth. Often if fluorescein treatment is used in cases considered inoperable, the induced changes make the case amenable to surgery.

PEDIATRICS

UNDER THE CHARGE OF

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The Period of Infectivity and Serum Prevention of Chickenpox.—GORDON, MEADER (*J. Am. Med. Assn.*, 1929, 93, 2013) state that preceding the eruption chickenpox is apparently infectious for only a brief period, probably not more than twenty-four hours. Infectivity during convalescence is less prolonged than commonly considered and does not necessarily coincide with the persistence of crusts. It probably lasts only ten days. Convalescent serum furnishes a high degree of protection if secured within one month of the period of the lesions. If the serum is obtained after a longer time it is progressively less efficient and after five months confers immunity only in about one-third of the immunized susceptibles. In their work to corroborate the reported results of the protective action of the serum, they used 10 cc. of a pooled serum from convalescents of from one to two months. The results were very satisfactory. In three outbreaks there were no secondary cases. In another outbreak, one of six immunized susceptibles developed chickenpox. These children were all under eight years of age and 11 were less than four years. The possibility that divided doses might give better results was not upheld on trial. In their experiments 55 of 81 susceptible children or 68 per cent developed chickenpox when serum was not used. It was seen from this that it is not logical to conclude that the absence of infection in the immunized group was entirely due to the use of serum as a certain appreciable proportion seemed to escape infection under all conditions. The duration of immunity is brief. Reëxposure of 12 patients from secondary cases resulted in 2 clinical cases. In administering the serum it was given intramuscularly into the lateral aspect of the thigh. There were no reactions. As far as could be observed the course of the disease in immunized patients was in no way modified nor was the expected incubation time appreciably affected.

The Early Diagnosis of Latent Heredodysphilia.—ALARCON (*Arch. d. Med. des. Enf.*, 1929, 32, 589) indicates a new clinical guide in the diagnosis of syphilis on the basis of a typical intestinal disorder occurring in children under three months of age. He calls this the transitional dyspepsia of infants. It is characterized by symptoms occurring during the first days of breast feeding. Shortly after feeding regurgitation and hiccough occur which at times may awaken the infant. The intestinal disorder is evidenced by crying. Vomiting is rare in breast-fed infants although frequent in artificial feeding. Acid diarrhea with erythema of the buttocks follows the initial constipation. The author divides the condition into a preliminary stage lasting three weeks, a secondary stage lasting six weeks and a final stage lasting three weeks,

and he feels that the influence of syphilitic septicemia on the nervous system is the most frequent cause. The early onset with the exaggerated symptoms and the prolonged duration are suggestive of the underlying lues.

The Size of the Reacting Area in Intracutaneous Tuberculin Tests.—DICKEY (*Am. J. Dis. Child.*, 1929, 38, 1155) studied 700 positive reactions to tuberculin. In these he found that the average area of the reaction was about 459 sq. mm. The size of the reaction varied widely in the group studied with the exception of that in very young children and of that in children having phlyctenular conjunctivitis. He observed no difference of the average size of the reaction in girls and in boys. There was a gradual increase in the size of the reaction from the first to the sixth year although this may not mean an increase in the degree of sensitization. Children of Oriental parentage were more sensitive than other racial groups. Children who had had contact with tuberculous persons reacted more strongly than children who gave no such history. He suggests a relationship between sensitivity and the extent of the markings in roentgenograms but he does not feel that there is any relationship between sensitivity and other roentgenologic observations. It was noted that children with phlyctenular conjunctivitis, lymph node, bone and joint tuberculosis reacted more strongly than those with hilar disease although the latter gave slightly stronger reactions than children suffering from an adult type of pulmonary tuberculosis.

Breast Feeding.—GERSTLEY (*Arch. Ped.*, 1929, 46, 749) in a series of breast-fed babies noted that in each baby the amount taken at individual nursings during the day were quite varied in contradistinction to the statements in textbooks that children take the same amount of food at each nursing. The variability of some of these observations is extreme. Not only varying in amounts at each feeding and thus giving an irregular twenty-four hour total so that no two days were identical. One of the most surprising observations made was the enormous quantity of milk taken by one of the babies at some of his nursings, even during the early months of his life. These observations were checked and were found to have been accurate. It was noted that during the fourth week of age this infant took as much as $8\frac{1}{2}$ to 9 ounces at a nursing. This was an extreme record. Gerstley feels that his figures show that it is impossible to standardize the diets of infants because their intake depends primarily upon their constitutional demands. He feels that this lesson should be remembered in bottle feeding. In this study the amounts of milk taken from each breast of the mother were also determined and in this series there was a greater output from the right breasts of the mothers not only in the case of an older child who nursed more vigorously but also in the younger child. The author feels that the stimulus of the nursing infant is a great factor in promoting secretion of milk but there may be individual variations in the breasts themselves.

The Kahn Precipitation Test in Infants and in Early Childhood.—CAFFEE and KREIDEL (*Am. J. Dis. Child.*, 1929, 38, 1206) feel that the Kahn test is a highly sensitive and specific serologic test in infancy and

early childhood and while it closely parallels the Wassermann reaction it is not identical with it. Positive Wassermann reactions are more easily reversed by antisyphilitic treatment than are positive Kahn reactions. The latter is considerably more sensitive than the former in mothers of syphilitic offspring. It is highly specific in mothers of nonsyphilitic offspring and equals the Wassermann test in this regard. It has decided advantages in simplicity as a laboratory procedure. In their study the authors believe that the Kahn test performed alone would have given somewhat more reliable information than the Wassermann performed alone but the performance of both complement fixation and precipitation test simultaneously on identical serums give more information than either test alone and affords a double control in serologic diagnosis.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Early Syphilis, Results of Treatment in Four Hundred and Forty-four Cases.—CHARGIN and STONE (*Arch Derm. and Syph.*, 1929, 19, 750) state that while there is no complete agreement among syphilographers on the best single plan of treatment, it is generally accepted that the treatment should be intensive and that the combination of arsphenamin with mercury or bismuth should be used. This constitutes the modern method of antisyphilitic therapy and although it has been employed only for about fifteen years, it has been in use a sufficiently long time to permit the evaluation of results. Chargin and Stone present an analysis of 444 cases of treated early syphilis in the period 1911 to 1926. The criteria of cure in this series and standards involved included the earliness of the stage at which the treatment was started; the use of at least one course of arsphenamine and one course of mercury or bismuth; the freedom from clinical recurrence while under treatment with a negative Wassermann at the end of treatment; observation for a least one and one-half years following the last treatment with no clinical recurrence during this period; and repeated negative Wassermans during the period of observation. The authors did not examine the spinal fluid in all cases (nor is mention made of physical reexaminations or special neurologic or cardiac studies, so that to this extent the data for decision as to cure are seriously incomplete). The cases were classified in four groups, primary seronegative cases, 36; primary seropositive cases, 55; early secondary cases, 267; and late secondary cases,

86. The plans of treatment employed were: (1) *The intermittent plan*, regular courses of arsphenamin and mercury or bismuth with alternating periods of rest of one or two months. In this group were 269 patients. (2) *The intensive plan* (Pollitzer), early saturation treatment of the patient with frequent and large doses of arsphenamin followed by a course of mercury or bismuth and concluded by a final course of arsphenamin. This was used in 16 patients. (3) *The mixed injection plan*, using a mixture of neoarsphenamin and mercuric chlorid in courses, with alternating periods of rest. Twenty patients were treated according to this plan. (4) *The continuous plan*, alternating course of arsphenamin and mercury without rest periods for as long as a year. This was used in 55 patients. (5) *The irregular plan*, as the name suggests, was used to designate a group of 85 patients treated without any organized or definite scheme. The term "course" as used by the authors means 6 to 8 injections of arsphenamin and 12 to 15 injections of mercury or bismuth. The dosage varied with the age and weight of the patient, arsphenamin averaging from 0.2 to 0.4 gm. per injection, and mercury or bismuth 1 to 15 cc. of the insoluble preparations (amounts of the salt not given). The majority of the patients in this series were treated with arsphenamin and the heavy metal concurrently, with rest periods between courses. The authors believe that continuous treatment is generally not well borne, and that rest intervals are desirable to permit elimination of accumulated drugs and to avoid toxic effects. In primary seronegative syphilis, 90 per cent of the patients were apparently cured within the inadequate standard accepted by the authors and one-third of the cured patients received but one course of treatment. The authors feel that the important factor in this stage is the early beginning of treatment rather than the amount or method employed, although it is noteworthy that the 4 cases receiving the intensive plan of treatment were all regarded as cures. Fifty-five cases of seropositive primary syphilis were treated, with 61 per cent of cures. Again the majority of cures in this group were in the patients receiving but one or two courses of treatment. The same percentage of cures, that is, 61, was obtained in 267 cases of early secondary syphilis, the majority receiving intermittent treatment and but one or two courses. Intensive treatment was employed in 8 cases with cures in all. Of the 86 patients in the late secondary group, cures were obtained in 45 per cent. A general consideration of treatment based on the number of courses showed surprising results. Cures were obtained in 74 per cent of those patients receiving but one course, 72 per cent for two courses, 54 per cent for three courses, 50 per cent for four courses and 28 per cent for five or more courses. The authors believe this apparent paradox is explainable by the fact that the failure of patients to respond after one or two courses augurs a poor outlook for cure after further treatment. (Are we to interpret that the authors advocate one or two-course treatment as a standard for cure in those patients who would "respond" during that period, or is their use of the term "cure" open to discussion?) Beyond the 100 per cent results achieved with the intensive plan of treatment (16 cases) the plans of treatment appeared equally efficient, cures ranging from 57 to 60 per cent. The authors feel, however, that the patient is benefited by employing a plan that includes rest periods, inasmuch as the chance for cure appears to be in no way diminished.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Menstrual Disorders Treated by Irradiation of Ovaries and Hypophysis.—It has been known for some time that irradiation of the ovaries and of the hypophysis very often has a definite effect on the menstrual flow and its disorders. FORD and DRIPS (*Radiology*, 1929, 12, 393) report on the clinical and experimental studies of low-voltage irradiation as conducted at the Mayo Clinic. They state that irradiation of the ovaries or hypophysis has been effective in reestablishing menstruation in patients in whom prolonged use of organotherapy had been ineffective. A conclusion cannot be drawn as to the comparative efficiency of methods because the cases selected for irradiation were of unusual severity. Irradiation of the hypophysis, occasionally combined with splenic and hepatic irradiation has exerted a temporary regulating effect in 7 cases of severe menorrhagia and metrorrhagia. Relief of dysmenorrhea has been incidental in certain cases of menorrhagia and oligomenorrhea. Of 6 cases treated primarily for dysmenorrhea, relief has been complete in 3 and has lasted for a period of four to six months; improvement occurred in 2 others. Irradiation of ovaries of white rats in various dosages produced no continued influence on the regularity of the estrual cycle. Complete destruction of follicles did not result from dosages up to 2.5-unit skin doses. There was no influence on fertility, except in cases in which there was marked systemic reaction, with irradiation of 50 per cent unit skin doses or below. With the application of $2\frac{1}{2}$ -unit skin doses sterility has been produced in 5 of 10 rats. Abnormality in the progeny has not been demonstrated. They state that a consideration of the mechanism by which small amounts of Roentgen rays, acting either on the ovaries or on the hypophysis, are able to reestablish cyclic menstruation and to relieve sterility would serve only to open theoretic controversy. The harmlessness of irradiation of the ovaries in low dosage seems to them to be sufficiently well established by all pertinent biologic studies and by the numerous instances of normal children being born to women who had previously been irradiated with even much heavier doses than those required in the treatment under consideration.

Results of Treatment of Cervical Cancer.—From the Gynecologic Clinic of the University of Kiel comes a report by CLAUBERG (*Zentralbl. f. Gynäk.*, 1929, 53, 2339) of 380 cases of carcinoma of the cervix which were seen between January 1, 1917, and September 30, 1922.

Of these cases, 107 were living and free from evidence of carcinoma at the end of five years; therefore, there is an absolute healing rate of 28.2 per cent. Some years ago the result of this clinic for the period of from 1910 to 1916 were reported by Giesecke and the following table which summarizes that report as well as the present series is of great interest:

	1910-16	1917-22
Total number	350	380
Operability, per cent	70.6	54.7
Number operated upon	243	160
Primary mortality, per cent	18.9	13.0
Operable cases:		
1. Wertheim	224	148
Primary mortality, per cent	19.6	14.2
Relative cure, per cent	33.5	43.2
2. Vaginal hysterectomy	19	12
Primary mortality, per cent	10.5	0
Relative cure, per cent	57.9	50.0
3. Irradiation	3	48
Primary mortality, per cent	33	0
Relative cure, per cent	67	43.7
Inoperable cases:		
1. Irradiation	60	150
Primary mortality, per cent	not given	6
Relative cure, per cent	8.3	10.6
2. Operative procedures	43	3
Irradiation	2
No treatment	17

It is of interest to note that the operability rate has decreased due to the fact that the irradiation percentage has markedly increased. Even though there is a very satisfactory reduction in the operation mortality in the second series this clinic has seen fit to subject an increasing number of patients to irradiation so that while there is still a large number of operations performed, the surgical treatment is becoming less popular as is the case in this country.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Amaurosis Following Ingestion of Ethylhydrocuprein.—Though ethylhydrocuprein is a quinin derivative and its use in pneumonia is growing, few cases of visual disturbances due to its use have been reported. ALVIS (*Arch. Ophth.*, 1929, 2, 328) presents a case of sudden amaurosis which must have been due to the disease since its course so resembled quinin amaurosis. In the course of three days the woman, aged twenty-two years, had been given 58 grains of ethylhydrocuprein at the rate of 4 grains every five hours. During the third night she lost her power to distinguish color and by morning she was unable to distinguish light. Two hours later she was entirely blind, the pupils

widely dilated and fixed. Five hours later ophthalmoscopic examination showed widely dilated pupils, disks very pale with slightly blurred margins, retinal arteries practically obliterated because they were so narrowly contracted; small and thread-like retinal veins. In the right macula there was a cherry spot in the moderately edematous retina. There was no such in the left. When seen by Alvis ten days later there was no change, though she could perceive light. Two months later the fundus was the same except that the cherry spot had disappeared and the edema was gradually clearing. She was able to count fingers at a distance of 8 feet in a fairly wide field. Four months after the attack the pupils were wide and reacted sluggishly to light. The patient saw everything through a purple haze which prevented differentiation of colors. Vision in either eye was 20/75. The visual fields were restricted between 15 and 30 degrees. As soon as the diagnosis of ethylhydrocuprein poisoning was made nitrites were given in increasing doses. Potassium iodid and pilocarpin was given for diaphoresis. Hot applications were made to the eyes. Later increasing doses of strychnin were administered. The author concluded that amaurosis from ethylhydrocuprein can occur in a severe form, though extremely rarely and that the treatment is without influence on the condition. Some permanent disability follows even mild cases of ethylhydrocuprein or quinin poisoning, varying with the severity of the intoxication.

Ocular Lesions in Tularemia.—There are four clinical types of tularemia in one of which conjunctivitis is the primary lesion and there is involvement of the regional lymph glands. This form usually shows multiple, small, discrete ulcers of the palpebral conjunctiva with indurated margins and yellow, necrotic plugs. There is pronounced chemosis and swelling of the lids and mucoid discharge. Swelling and tenderness of the regional lymph glands is present, the fever is intermittent, the convalescence prolonged. JUDD (*Arch. Ophthalm.*, 1929, 2, 300) reports 2 cases of the ocular type of tularemia. The first case was typical, the second atypical for swelling of the axillary glands preceded the ocular trouble and dendritic keratitis appeared; this latter has apparently not previously been reported. The eyes in the first case soon recovered, being treated with instillations of 1 per cent mercurochrome-220 soluble, corrosive mercuric chlorid ointment 1 to 2000 and hot applications, and moderate doses of salicylates. The second case, when seen, presented conjunctival congestion and circumcorneal injection. There were several dotlike areas on the upper, inner quadrant which stained with fluorescein; in the pupillary area there were several thin nebula. A mild iritis was present. There was no swelling of the regional lymph glands. The eye was treated with hot, moist applications, atropin, 1 per cent mercurochrome, corrosive mercuric chlorid ointment and was kept bandaged. The dots had coalesced by the fourth day, forming a typical dendritic ulcer on the upper, inner part and across the cornea below the pupil. Slight inflammatory infiltration in the superficial layers of the stroma beneath the epithelial lesion, but no keratitic precipitates, were shown by the slit lamp. There were no stains by the tenth day. Vision which at first had been 20/100, became 20/50 with correction. There has been no recurrence.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Vertigo.—The symptoms of vertigo are well known, yet much remains for the clinician to study and learn, and for the scientist to survey and explain. Patients who have had both labyrinths completely removed or who have bilateral auditory nerve tumors involving the whole of each eighth nerve and deaf-mutes who have complete loss of function of the vestibular nerves, do not suffer from vertigo. On the other hand, normal persons can become dizzy without any physical disturbance of the labyrinth—reminding us that every case of vertigo is not necessarily labyrinthine in origin. Defining vertigo “as the state of consciousness of a false sense of orientation of ourselves in relation to our environment,” SCOTT (*J. Laryngol. and Otol.*, 1929, 44, 429) after mentioning labyrinthitis, otitis media and otosclerosis as aural conditions which not uncommonly give rise to giddiness, emphasizes the association of recurrent vertigo with inefficiency of the Eustachian tubal mechanism. In discussing vertigo among aviators, he states that all pilots should be capable of inflating both Eustachian tubes by Valsalva’s method, or of opening them by the act of swallowing before they should risk high flying. Other causes of vertigo, such as reflexes from conditions affecting the fifth nerve, syphilis, and disseminated sclerosis, are enumerated.

Pathologic Changes in Tonsils. A Study of Ten Thousand Pairs of Tonsils, with Special Reference to the Presence of Cartilage, Bone, Tuberculosis and Bodies Suggestive of Actinomycosis.—WILKINSON (*Arch. Otolaryngol.*, 1929, 10, 127) makes a comprehensive statistical and analytical report based on the findings of a histopathologic study of ten thousand pairs of tonsils removed consecutively at the Mayo Clinic from 4616 females and 5884 males with a true average or mean age of 33.56 years and a standard deviation, or spread of the material, of 17.7 years (probable error of 0.1 year). Following fixation in a 10 per cent solution of formaldehyde, each tonsil was bisected horizontally and a frozen section from the bisected surface of each tonsil was mounted and stained with hematoxylin and eosin. After a complete compilation of the data in the 10,000 cases, it was found that all tonsils showed evidence of chronic infection, if the presence of leukocytes in the crypts and ulceration of the epithelium are indications of infection. However, in only 14.27 per cent of tonsils were there “pathologic changes of bizarre types.” Cartilage and bone occurred in various grades and proportions in 11.21 per cent, cartilage predominating. Fibrosis was relatively increased in those sections showing cartilage and bone. The author believes that chronic infection is a great and definite factor in the production of fibrosis, bone and cartilage although he recognizes that

fibrosis can increase independently of infection and in direct relationship to age. Actinomycosis-like granules were encountered in 1.77 per cent. Tuberculosis of the diffuse type had an incidence of 0.52 per cent, in 0.17 per cent of which the involvement was bilateral. Trichinae were identified in 0.06 per cent of the extirpated tonsils, occurring in the capsular or septal tissues. The author concludes that "there is sufficient pathologic change of interest in the tonsils to warrant routine microscopic examination of removed tonsils."

Pathogenesis of Sepsis Following Angina. Histologic Observations of the Material from 26 Patients of Professor Claus, Berlin.—In the microscopic examination of the tissues from 26 cases of postanginal sepsis—11 of which came to postmortem and in the other 15, surgically removed tonsils were available for study—BURCHARDT (*Ztschr. f. Hals-, Nasen- u. Ohrenheilk.*, 1929, **23**, 97) stressed the common occurrence of perivascular infiltration, which began in the tonsillar tissue and could be traced (in the necropsical material) to the larger regional veins. In five instances in which the presence of sepsis was not entirely convincing the vascular lumina were clear, although a lymphangitis was observed. Some cases exhibited lymphadenitis and suppurative thrombophlebitis. Often all the layers of the bloodvessel walls showed inflammatory changes. On one occasion medical disintegration was found in the absence of demonstrable intimal inflammation or thrombosis. The author believes that the presence or absence of a thrombophlebitis plays a minor rôle insofar as the actual genesis of postanginal sepsis is concerned.

RADIOLOGY

UNDER THE CHARGE OF

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Radium Therapy.—The entire March issue of *The Radiological Review* (1929, **51**, 93-140) is devoted to radium therapy. In the first paper PFAHLER relates his experience in the treatment of *cancer of the mouth*. It is painless at the time of application, though it causes soreness and swelling of the mouth at the height of the radiation effect; it requires no anesthetic, no hospitalization, and produces neither mutilation nor constitutional symptoms: in tongue cases the function of the tongue is preserved; it usually causes metastatic lymph nodes to disappear. Of a total of 56 advanced intraoral cancers with glandular metastasis treated during the past three years, 36, or 64 per cent, are living; 23, or 41 per cent, are clinically cured, and 13 are still under treatment.

HENRIQUEZ has had success in the treatment of *hypertension*. The method consists in the application of 50 mg. of radium to each side of the skull at a point just in front of and a little above the external auditory meatus. The radium is filtered by 2 mm. of brass and is at a distance of 1 inch from the skin. One hour's application, repeated weekly until the pressure falls, is considered best. Diastolic pressure has been lowered over 20 mm. in certain cases, the enlarged heart has been reduced in size, and the patients have improved subjectively.

Plantar warts were treated successfully by COSTLOW in 20 cases. In 15 only a single treatment was required.

Of 9 cases of *adenocarcinoma of the cervical canal*, treated by SCHREINER, 1 is alive and well after eight years; 1 died in four years from intercurrent disease after being well for three years; 1 died after one year of palliation, and the remainder died of recurrence and metastasis. In 50 per cent of the operable cases of *cancer of the fundus* the patients are healed alive and well after more than five years: in the inoperable cases no patient survived five years.

SWANBERG has used a modified cervical applicator for the Regaud technique in *cancer of the cervix*. He believes that surgical treatment should be abandoned since better results are secured by irradiation. Statistics show that 72 per cent of cervical cancers, representing all stages, are living one year after irradiation, with 27 per cent free from the disease after five or six years.

According to MURPHY and MURPHY, all patients with *cancer of the skin* can be cured by radium, without pain, loss of time or disfigurement, if properly irradiated while the lesion is confined to the integument.

TYLER reports a case of *osteogenic sarcoma* of the humerus treated by radium and Roentgen rays, in which the destroyed bone was largely regenerated and the patient is in apparent good health after one year.

LENTH regards radium therapy as the treatment of choice in *epithelioma of the lip*, because there is less inconvenience, loss of function and disfigurement than from any other form of treatment and it yields a higher percentage of cures. Palpable lymph glands should be treated by radium and resected if unimproved.

Roentgen Ray Diagnosis of Lesions of the Small Intestine.—For examination of the small bowel SOPER (*Am. J. Roent. and Rad. Therap.*, 1929, 12, 107) employs a special technique: (1) The patient must be examined in the upright posture. (2) Abnormalities in the small intestinal pattern should be sought for from two and a half to six hours after the opaque meal is given. They are often demonstrable about the time the last part of the barium meal leaves the stomach. (3) Make films of suspicious areas at once, and continue to watch for other anomalies. Shadows are likely to be evanescent; the examiner should remember that he is searching for evidence of partial and not complete obstruction.

The shadows produced by peritoneal tuberculosis are bizarre and irregular in character and portray the various scattered dilatations and contractures of intestinal loops. Metastatic carcinoma of the peritoneum and intestine produces a similar picture. Primary cancer of the small bowel may produce a pseudodiverticulum but it is more irregular than a true diverticulum, and the shadow of the latter persists

for a much longer time. Shadows resulting from adhesions are instructive; atypical patterns may be found in nearly all patients who have been subjected to abdominal section. Strong bands of adhesions may cause periodical attacks of partial obstruction with dilatation of the loops. A gas-bubble above the barium level is a frequent finding. Twenty-four-hour stasis in the ileum must be regarded as pathologic; of course, its presence twenty-four hours after the meal may be due to pyloric obstruction. Extraalimentary growths may cause obstruction or distortion by pressure or adhesions.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

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Les Tumeurs du Quatrième Ventricule et le Syndrome Cerebelleux de la Ligne Mediane.—VAN BOGAERT and MARTIN (*Revue Neurologique* 1928, 2, 431) present 12 cases of tumors of the fourth ventricle with a clinical study for the purpose of developing diagnostic criteria. They conclude from their observations that the fourth ventricle tumors have a very rapid onset with rapid early development. The headache is usually very precocious with cramps in the neck, vomiting, vestibular or tonic attacks and certain modifications of attitude and epigastric or segmental pain and symptoms of the involvement of the vermis, (ataxia, asynergia, dysmetria) very often unilateral. The papillary edema appears and the patient adopts his typical attitude. This is due to a block of the cerebrospinal circulation. Later there appear bulbar symptoms, syncope, pseudoanginal crises, pseudoasthma, episthotonic crises, irregularity of the pulse and of the respiration, attacks of apnea, generalized crises of sweating with sometimes glycosuria. The function of the cranial nerves is rarely involved and disturbances in these cases have no localizing value. The complete evolution of the cases is very rapid, from six to ten months. Very rapid death is frequent, at times on the operating table. Ventricular puncture will relieve the pressure on the bulb and may allow the patient to survive. In detail the interesting symptomatology is the early onset of paroxysmal headache and painful radiation to the neck, the shoulders or the arms. These headaches are accompanied by two phenomena, an objective rigidity of the muscles of the neck and sometimes of the trapezius with an attitude of hyperflexion and often a lateral deflection of the head in an attempt to reestablish the hydraulic equilibrium of the posterior cerebral fossa. This is due to a blockage of the cerebrospinal circulation, which can be demonstrated and was demonstrated in 3 of their cases by graphic

determination of the cerebrospinal-fluid pressure. In these cases the blockage was partial, was increased by hyperextension and decreased by flexion of the neck. Hence they consider this position of flexion as representing a reaction in an attempt to reestablish the hydraulic equilibrium in the cranium. They found that brisk movements of the head may give rise to crises of variable gravity, from simple minor disturbances to a fatal syncope with apnea. In addition they find early disturbances of the genitourinary functions which they consider as symptoms of involvement of the median fasciculus. Disturbances of gait are not marked in the early stages but are usually mildly present throughout the inferior members and coördination is conserved in the arms. Following the early symptoms we have a state that is characterized by a syndrome of general hypertension and by the appearance of localizing signs. This begins very rapidly and a double papillary edema is quickly developed, hence we may have labyrinthian excitation, transitory diplopias, digestive disturbances, etc. The marked hypertension of the posterior cerebral fossa is manifested by ventriculography which shows marked internal hydrocephalus, and clinically it is shown by the symptoms of meningeal irritation. The tumors affect the subcerebellar pontine quadrilateral. They are directly adjacent to the main afferent and efferent paths of the cerebellum, the lateral and median bundles of Reil and the vermis, hence the symptoms of cerebellar involvement and especially of involvement of the vermis are present. A large majority of the patients complain of disturbances of equilibrium in gait and station. The progression is characteristic and retropulsion is frequent. The asynergia of Babinski and decomposition of movements are present in many cases in a classic manner. One sees in many cases hypermetria, slowing of the preterminal movements, intention tremor, and adiadochokinesis. Disturbances of writing, reading and speech are generally absent and proprioceptive reflex disturbances are exceptional. Bárány tests are not of value because they are rendered uncertain by the hypertension of the posterior fossa. The function of regulation of the muscle tone is much disturbed and to this disturbance is attributed the tonic attacks (cerebellar fits of Jackson) and the hypotonicity of the muscles and loss of tendon reflexes. The tonic attacks do not occur in all tumors of the fourth ventricle or in all of the median cerebellar line but when they are observed they have great localizing value and are symptoms of serious import. They have been found in lesions of other locations such as tumors of the angle, of the peduncle and of the pons. The picture is that of tonic contraction with hyperextension of the entire body, hyperextension and pronation with adduction of the superior members, trismus, Cheyne-Stokes respiration and irregularity of pulse. The face is pale, the tendon reflexes are abolished, the corneal reflex and pupillary reflexes to light are frequently absent. The head may be deviated to the opposite side or to the side of the body where flexion is manifested. The eyes are turned upward, at times laterally to the side where hyperextension is most marked. The rectal temperature is not increased during the crisis. Consciousness may be abolished but not always completely so. The attack may predominate on one side of the body and give rise to a turning of the body which causes the paroxysmal syndrome of torsion about the longitudinal axis of the body. This syndrome has been

observed in other lesions of the cerebellum. The combination of tonic attacks of torsion and the opisthotonic crises with hyperactivity and confusional states has been confused with hysteria. Between the attacks the tendon reflexes are abolished and many of the patients present hypertonicity with the abolition or enfeeblement of certain tendon responses. This abolition of reflexes is explained by the influence of the tumors of the fourth ventricle on the rubrospinal and reticulospinal tracts while the corticospinal inhibition persists. Certain minor symptoms and very rare symptoms have been observed. The signs of grave concern are the tonic attacks, the bulbar attacks and the negative Quackenstadt tests. The presence of one of these symptoms indicates the urgency of intervention. The phase of decline is characterized by the presence of the increase in the bulbar symptoms and is frequently followed very shortly with death. The bulbar symptoms are primarily tachycardia of extreme irregularity, alternation vasoconstriction and vasodilation of the face, dyspnea with polypnea or Cheyne-Stokes respiration, polyuria, sweating, and so forth. The irritation of the meninges is manifested by very violent pain of the neck with Kernig sign. At this time a lumbar puncture or a surgical intervention may be fatal. Therefore, one should not intervene during a bulbar crisis. Grave symptoms have occurred at the very beginning of anesthesia. They find it impossible to differentiate diagnostically, tumors of the fourth ventricle from endotheliomata of the recess, lateral bulbar gliomas, simple cerebellar bulbar cystic arachnoiditis, and so forth. Tumors of the hemispheres are often very slow in development. The cerebellar symptomatology appears early and this symptomatology remains for a long period unilateral. Also in the hemispheric tumors the vestibular attacks and a reflexia are very rare as are the tonic attacks which have only been reported in a single case of glioma of the hemisphere. In all other cases these attacks have been seen in lesions of the vermis or the pons. The pathologic findings in their cases are interesting but will not be abstracted here. Surgical intervention is recommended and a simple approach to the posterior fossa, using local anesthesia is recommended.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Dental Caries.—In studies of dental caries much attention has been given to the possible etiologic importance of certain aciduric bacteria. MORISHITA (*J. Bacter.*, 1929, 18, 181) has found the presence of such organisms to be almost constant in the tooth enamel in the early stages, and also in the saliva of persons with carious teeth, but relatively rare

in those without dental caries. He found no definite proof, failing positive *in vivo* experiments, that they were directly responsible. The variation or pleomorphism found in the group makes it difficult to classify the bacteria found by others. The author, however, considers, because of the relatively high acidity produced, that these bacteria are probably associated in an intimate way with the disease.

Involvement of Medium-sized Arteries Associated with Syphilitic Aortitis.—SAPHIR (*Am. J. Path.*, 1929, 5, 397) reports the results of a study of the proximal portions of the medium-sized arteries in 50 individuals presenting syphilitic aortitis. The object of the study was to find the early stages of syphilis in arteries which resembled the aorta structurally. For the purpose of this paper he grouped the innominate, carotid, subclavian and common iliac arteries as having an excess of elastic tissue and the superior mesenteric, inferior mesenteric, and femoral arteries as representing the muscular type of artery. The arteries of the elastic group were involved much more frequently than those of the muscular type. The majority of the lesions were found in the adventitia and in the intima. The changes in the adventitia consisted of endarteritis of the vasa vasorum and perivascular infiltration of lymphocytes and plasma cells. This lesion he interpreted as early syphilis. He was unable to determine whether the lesion primarily present was the endarteritis or the perivascular infiltration. The significant lesions of the intima were circumscribed button-like areas of fibrosis without degenerative changes. While these are not specific in character they were found most frequently at the site of syphilitic lesions in the adventitia. The media of the elastic type of arteries showed interruption of the continuity of the elastic fibers and fibrotic areas combined with circumscribed lymphocytic infiltrations. The media of the muscular type of arteries only rarely showed changes, which were confined to the outer portion of this coat where most of the elastic fibers are present.

The Rôle of Clasmatoocytes in Protection Against Pneumococcus.—CLARK (*Arch. Path.*, 1929, 8, 464) reports experiments on rabbits in which a mobilization of cells in the pleural cavity had been effected by the injection of aleuronat starch. Eighteen hours after this preparation, the cellular response is predominantly polymorphonuclear, while in a seventy-two-hour preparation the exudate is chiefly mononuclear, the pleural wall is thickened, filled with granulation tissue and many macrophages. The eighteen-hour preparation afforded no protection against a virulent strain of pneumococcus Type I injected into the pleural cavity nor against pneumococci that had been in contact with small amounts of antiserum. Seventy-two-hour preparation afforded no protection against pneumococci of the same strain, washed or unwashed; however, this preparation did confer marked protection against pneumococci that had been in contact with immune serum. The animals survived doses ten to a hundred times that which was fatal for normal rabbits on eighteen-hour preparations. It is concluded that there is a definite correlation between accumulation of clasmatoocytes and resistance to pneumococcus infection in the pleural cavity of the rabbit.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Meningococcus Meningitis and Measures for Its Control.—McCoy (*United States Pub. Health Rep.*, 1929, 44, 1595) refers to the exceptionally high prevalence of meningitis during the past year. The disease has been more prevalent in the West than in the East. Some cases have been fatal in as little as four hours, and the author reports a case fatal in twelve hours and another in twenty-five hours. It is pointed out that it is often not recognized that cases may occur without characteristic symptoms of the nervous system and that these cases may be established only by isolation of the organism from the blood stream or by its identification in skin lesions. Serologic types of the meningococcus are briefly discussed and it is pointed out that all types may prevail in the same epidemic and that they have no relation to clinical manifestations or to epidemiology. Clinical reports are cited to show that the serum available may usually be expected to give favorable results, though it is pointed out that the standardization of the preparation is on a most unsatisfactory basis. Under control measures the opinion of various authorities are noted and their conflicting nature emphasized. The control and disinfection of carriers are regarded as impracticable and it is pointed out that most carriers clear up in a few days regardless of what is done or is left undone. The writer closes with the following quotation from Rosenau: "It is not clear that any of the measures so far taken have either materially influenced the course of epidemics or prevented the spread of the disease."

A Study of Endemic Pellagra in Some Cotton Mill Villages of South Carolina.—GOLDBERGER and his colleagues (*United States Pub. Health Rep.*, 1928, 43, 2645) make the following observations on a group of 22,653 persons among whom 1147 cases of pellagra were observed, an incidence of 50.6 per 1000. Of the 4104 households among which that population was distributed, 18.5 per cent had at least one member affected by the disease in that year. Pellagra (in an endemic locality) is very much (two to six times) more prevalent than the experience of the physicians of the locality would seem to indicate. The fatality rate of the endemic disease, when definitely marked cases of all grades of severity are considered, would appear not to exceed 3 per cent. Striking peculiarities of age and sex distribution of the disease were observed. The observations of age incidence appear to indicate, what seems not to have been recognized heretofore, that endemic pellagra is prepon-

deratingly a disease of children of from two to fifteen years of age. Explanations of the peculiarities of age and of sex incidence are suggested. The single woman, as compared with the married, widowed, or divorced, is relatively exempt from the disease. In the population group under consideration, the single woman is usually a wage earner, which may place her in a somewhat more advantageous position with respect to diet than her married or widowed sister. The incidence of the disease was found to be markedly seasonal; 80 to 90 per cent of all cases had their "onset" within the period April to July, inclusive. One explanation suggested, in view of the proved dietary relation of the disease, is the variation in diet brought about by the seasonal modification of the food supply. The seasonal incidence of cases distinguished by their occurrence singly or otherwise in a household, and as initial and recurrent attacks, was studied. The disease was found to have a marked and very sharply limited season of prevalence the curve of which, with a slight lag, paralleled that of incidence. The study failed to disclose any consistent correlation between sanitary conditions and pellagra incidence. Such association as may at times be observed is regarded as accidental and to be explained by the intimate relation of the endemic disease to economic status, of which the sanitary condition may be an index. The study reveals the existence of a striking inverse correlation between the incidence of the endemic disease and family income. The continuous study of a selected village during a period of nearly six years appears to demonstrate that income shortage was a fundamental, though indirect, controlling factor in relation to the year-to-year fluctuation in the incidence of the disease. It is therefore inferred that the year-to-year fluctuations in the incidence of the endemic disease are bound up with fluctuations in economic conditions that influence the ability of a certain section of the population to procure an adequate diet. Marked seasonal variations in the food supply of a selected village are demonstrated. A relation of this variation in food supply to the striking seasonal incidence and prevalence of the disease is suggested.

Seasonal Variation of Diphtheria Antitoxin Content of the Blood of Adults and Adolescents.—PERKINS, HEEREN, MEGRAIL and GROSSMAN (*Am. J. Hyg.*, 1929, 10, 13) have shown that a sample of school boys from eleven to fourteen years of age living and going to school in a crowded district has a definite picture showing low diphtheria antitoxin content in the late winter and in the spring, whereas a sample of adults whose occupation brings them into conditions of exposure not too dissimilar shows a totally different picture. No evidence has been found which might indicate that the normal autumn rise in diphtheria incidence is related to the antitoxin content of the blood of these individuals; the drop in incidence in late summer coincides with the general rise in antitoxin content in the series, but in view of the negative correlation at the time of increasing incidence it is at least questionable whether the recorded observations are significant. The work confirms Fitzgerald in demonstrating the existence of adults with practically no antitoxin in the blood and shows also that there may be a certain number of adolescents with similar characteristics. The authors believe that

additional studies of other groups will help to develop a picture of the cross section of antitoxin content of the general population, and even lead to appreciation of the part it plays in diphtheria incidence. They also state that it seems to them that this investigation strengthens the probability that the fundamental factor in seasonal variation in diphtheria is a modification of the resistance of the individual at the actual portal of entry.

The Schick Test in Palestine, a Country of Low Diphtheria Prevalence.—MANN and KLIGLER (*J. Prev. Med.*, 1929, 3, 309) claim that diphtheria and scarlet fever are relatively far less prevalent in Palestine than in countries having a temperate climate. From about 3000 Schick tests it appears that the percentage of diphtheria immunes at the ages above eight years in Palestine is the same as found by Zingher in New York City, but that the immunization starts earlier among the Palestine children than in the New York children. A comparison of the native and foreign-born groups on the one hand, and the Ashkenazic and Sephardic communities on the other indicates that the native-born, especially in the Sephardic community, develop their diphtheria immunity much earlier than the foreign-born children. It would seem, therefore, that the absence of diphtheria in Palestine is only apparent. Since active immunity can probably be acquired only as the result of infection, the infection rate in the early age groups must be relatively high to produce so large a number of immunes.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 20, 1930.

Unusual Urinary and Blood Findings in a Myxedematous Dog.—DAVID L. DRABKIN and C. S. WAGGONER (from the Department of Physiological Chemistry, University of Pennsylvania). It seems of interest to report a number of unusual findings upon a dog which has been under observation since its birth, more than three years ago. The dog was born in the laboratory and has always lived in a metabolism cage. Except for a period of about two weeks, during its early puppyhood, it has been maintained exclusively on Cowgill's synthetic diet.¹ At the age of two months it was thyroidectomized, the upper pair of parathyroids being left intact. An exploratory operation six months later insured the completeness of thyroidectomy.

Shortly after the second operation the urine of this animal, collected in the usual fashion, was observed to turn black on standing. Preservation of the urine under toluene delayed the color change, but did not

¹ Cowgill, G.: *J. Biol. Chem.*, 1923, 56, 725.

prevent it. All the usual qualitative tests for homogentisic acid were positive. Very small amounts of crystals characteristic of the lead salt and dibenzoyl derivative of homogentisic acid have been obtained. The writers have not, however, succeeded in preparing from the urine sufficient amounts of pure homogentisic acid for analysis. For about one year the dog daily continued excreting urine which turned black on oxidation. During the past six months the phenomenon has become increasingly less constant and has been observed only occasionally.

Another finding, perhaps of even greater interest, was made by chance. For the past two years determinations of the "hemoglobin" by the acid hematin content (determined by Newcomer's method and spectrophotometrically) or by Stadie's cyanhemoglobin method have been found to be 8 to 15 per cent in excess of the hemoglobin, calculated from determinations of the oxygen capacity of the blood by the method of van Slyke or by determinations of oxyhemoglobin spectrophotometrically. An observation of this type is presumably rare, although recently somewhat similar observations have been made following splenectomy.¹

Surface Properties of Chylomicrons.—R. L. NUGENT (from the Gladwyne Research Laboratory, Gladwyne, Pa.). General consideration lead to the hypothesis that chylomicrons in human blood serum are surrounded by films of serum protein. This hypothesis has been substantiated by two lines of experimental evidence involving the determination of the pH of the maximum isoelectric flocculation of chylomicrons in human serum and their behavior when gradually increasing amounts of protein precipitants are added to serum.

The probable importance of such protein films has been pointed out.

Double Chronaxie of the Nerve-muscle Complex.—W. A. H. RUSH-TON (from the Physiological Laboratory, Cambridge University, and the Johnson Foundation, University of Pennsylvania). The temporal aspects of tissue excitation were discussed, with especial reference to the value of the chronaxie as a measure of them.

It was pointed out that the usual method of chronaxie measurement, namely, by the determination of only two threshold points, might give rise to serious errors where the tissue had more than one kind of excitable element present.

Experiments were then described affording strong evidence that in the normal frog's muscle there are two excitable substances with very different time relations.

1. The excised sartorius in equilibrium with the Ringer fluid through eighteen hours' immersion was excited for various durations by passing currents of various strengths in parallel lines through the whole fluid.

The nature of the strength-duration curves depended upon the angle between the muscle fibers and the direction of the current. The curve, in general, showed two components, one of chronaxie 0.3 sig., the other 7 sig., and the proportion in which these two entered could be varied at will by changing the angle.

¹ Stimson, B. B.: J. Biol. Chem., 1927, 81, 62. Ray, G. B., and Isaac, L. A.: J. Biol. Chem., 1930, 85, 519.

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1. The excised sartorius in equilibrium with the Ringer fluid through eighteen hours' immersion was excited for various durations by passing currents of various strengths in parallel lines through the whole fluid.

The nature of the strength-duration curves depended upon the angle between the muscle fibers and the direction of the current. The curve, in general, showed two components, one of chronaxie 0.3 sig., the other 7 sig., and the proportion in which these two entered could be varied at will by changing the angle.

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2. The same two curves could be obtained by stimulating a region not far from the pelvic end of the freshly excised muscle. When the cathode was toward the pelvic (nonneural) region the lower curve was more prominent; reversal of the current gave greater prominence to the other, which was also shown to have the same chronaxie as the nerve trunk directly excited.

3. A small strip of muscle with parallel fibers from the sternocutaneous of the bullfrog was excited at different angles and various durations. Analysis by polar coördinates showed there to be two excitable substances; the fibers of one lay in the same direction as those of the muscle, the other at right angles. The former had the long chronaxie, the latter the short.

To Summarize. The nerve-muscle complex contains two substances of widely differing chronaxie. The first has the same time relations as nerve (as Lapicque claims for muscle) but the fibers run at right angles to the muscle fibers. The second substance has a chronaxie over twenty times as long and lies in the same direction as the muscle fibers.

The Use of Thiocresol to Stimulate Wound Healing.—S. P. REIMANN (from the Research Institute of the Lankenau Hospital, Philadelphia). Since cell division is impossible unless sulphur is present in the nucleus in the $-SH$ form, it is reasonable to suppose that the application of sulphhydryl compounds will accelerate cell division. Healing of wounds is done by cell division. Of the many possible compounds, thioglucose was tried first. It stimulated healing but it also stimulated bacteria.

Thiocresol was then tried with the idea that the $-SH$ part of the molecule would stimulate cell division and the cresol portion would tend to inhibit bacterial growth. These expectations were realized and thiocresol did accelerate wound healing. A number of practical points must be considered in the use for clinical purposes.

The main interest of the members of this Institute lies in the fact that cell division is stimulated by sulphhydryl.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1930

ORIGINAL ARTICLES.

THE CLINICAL SYNDROME OF HYPERPARATHYROIDISM.

By DAVID P. BARR, M.D.,

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AND

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MEDICINE.

(From the Medical Clinic of Barnes Hospital.)

Experimental Hyperparathyroidism. Following Collip's¹ discovery of an active parathyroid hormone, it became possible to study hyperparathyroidism experimentally. Collip² himself has summarized the effects of the injection of too much parathormone. The essential characteristic is hypercalcemia, sometimes exceeding 20 mg. per 100 cc. of serum. This develops rapidly, reaching a maximum in twelve to twenty-four hours, and falling as quickly as it arose. Symptomatically there is restlessness, respiratory distress, vomiting, diarrhea and, later, hematemesis and melena, collapse and death. There is usually hematuria, and in the fatal cases the kidneys cease to function about the time that the maximum value of hypercalcemia is attained. During this terminal period phosphates and nonprotein nitrogen of the blood rise rapidly; there is a decreased blood volume, thickening of the blood and a decrease in coagulation time which makes it difficult to obtain samples of blood for analysis. At autopsy there are hemorrhages into the kidneys and into the walls of the stomach and small intestines.

Almost immediately after Collip's preparation became available, Greenwald and Gross³ studied the effects of toxic doses of parathormone. Giving to dogs amounts which caused death in about six days, they observed not only hypercalcemia but also a great increase in the excretion of calcium accompanied by an excretion of phosphorus that increased independently of the greater protein metabolism. Later

these same workers,⁴ fearing that the changed excretion of phosphorus and calcium might be due to the severe intoxication rather than to a specific parathyroid effect, conducted a long-continued experiment in which parathormone was given daily for a period of almost two months. Under these circumstances, also, there was an increased excretion of phosphorus and calcium. The authors conclude that an abnormally high excretion can continue for a long period and that the calcium must be derived from bones, since no other tissue contains an amount sufficient to supply the 2.5 to 3 gm. of extra calcium which they found to be excreted during a fifty-five-day period.

Hueper⁵ observed metastatic calcification in the lungs, kidneys, stomach, duodenum, heart muscle and, what is more surprising, in the thyroid gland. Accompanying these changes there were calcium casts in the tubules of the kidneys, multiple small hemorrhages in the brain, many thrombi in the small vessels of the myocardium with areas of localized necrosis and fragmentation of fibers. In one cat he found necrosis in the cortex of a suprarenal gland.⁶

Since the hypoparathyroidism of tetany is characterized by an increased tone and irritability of muscles, one might expect that hyperparathyroidism would be accompanied by the opposite condition of hypotonicity and diminished irritability. Collip² mentions the apathy of dogs which have received overdosage. Edward and Page,⁷ who studied the effects of parathyroid extract on the heart, found incidentally that there was depression and in a few instances an "unmistakable atonia" of skeletal muscles. Berman,⁸ using galvanic currents, demonstrated a definite decrease in the electrical response of the peroneal nerve of normal dogs after a moderate increase in serum calcium produced by parathyroid extract. Looney⁹ was able to control muscular rigidity in patients with catatonic dementia precox by administering parathormone. In a series of eleven cases showing various degrees of rigidity he found a slight decrease in serum calcium. When the calcium in the serum was increased and maintained at a higher level with parathormone there was a decrease in muscle rigidity. Whereas before the injection it was impossible to open the patient's hands, afterward almost complete extension was obtained. It is of interest that Shohl¹⁰ and his associates observed a diminishing electrical excitability in the muscles of a child who while suffering from infantile tetany was given small doses of parathormone. The improvement in the muscular condition roughly paralleled a return of the blood calcium to normal.

Hyperplasia of the Parathyroids. In man, as in many other animals, there is great variability in the number, location and size of the parathyroid glands. Mere size is not always a sufficient criterion to establish the presence of hyperplasia or hypertrophy. Cowdry¹¹ offers as average measurements 6 by 3 by 2 mm., with an average combined weight of 550 mg., but states that no two investigators ever give the same figures. Many German observers have used the range suggested by Biedl, who considered a length of 3 to 15 mm. and a breadth and thickness of 2 to 4 mm. as the limits of normal variation.

In the individual case, where enlargement is not great, it may be necessary to depend upon slight changes in the microscopic picture which, even in the hands of the best pathologists, offers great difficulties. It is quite possible, moreover, that in the parathyroid, as in

some other organs, functional dyscrasia may not always be reflected in recognizable anatomic changes. In spite of these difficulties, an undoubted hyperplasia of the parathyroids has been found, experimentally, under a great variety of conditions.

Erdheim,¹⁴ in his monograph, described it in the spontaneous rickets of rats. Marine¹⁵ found hyperplasia of the parathyroids of fowls on a low-calcium intake. Recently Higgins and Sheard¹⁶ have found that enlargement of the parathyroids occur when either the longer or shorter waves of sunlight are deficient. Under these circumstances, the addition of cod-liver oil to the basic diet tends to maintain the glands at a more nearly normal size. They have also observed that after a few weeks of enlargement regressive changes with cyst formation may occur.

Susman¹⁷ has produced enlargement of the parathyroids by repeated injection of guanidin, his evidence being based on microscopic examination. After extirpation of part of the parathyroids it has been shown that the remaining tissue undergoes hyperplasia or hypertrophy. This was shown to an unusual degree in experiments of Tanberg,¹⁸ where all but one parathyroid gland was removed.

These experimental studies indicate an inherent power of the parathyroid glands to increase in size under a great variety of stimuli. Usually the enlargement is due to hyperplasia and not to hypertrophy of the individual cells.

In man, also, hyperplasia has been observed many times and under a great variety of circumstances. Sometimes it has been reported as hyperplasia or hypertrophy, but perhaps quite as often as tumor of the parathyroid. The dividing line between hyperplasia and tumor formation cannot always be sharply drawn. Ewing¹⁹ has expressed it concisely: "In several cases," he says, "the hyperplasia has been regarded as adenomatous." The microscopic differentiation being very difficult, there is always a tendency in the literature to designate the condition as adenoma when one gland is much larger than the others, and to label it hyperplasia when several or all of the parathyroids are enlarged. It must also be remembered that there are in addition true benign tumors as well as a few which are highly malignant.

Incidence of Hyperplasia and Tumors. Parathyroid tumors have been recognized since Kocher,²⁰ in 1899, suggested such an origin for 5 glycogen-containing tumors which he had observed in the region of the thyroid gland. Whether or not these were truly of parathyroid origin, Kocher's report served to introduce the subject. Langhans²¹ found 4 cases of similar character and De Quervain²² reported 1. It is interesting that in these early tumors both thyroid and parathyroid tissue was found. On the other hand, De Santi's²³ tumor and Benjamin's²⁴ huge swelling (the size of a child's head) appeared to have a purely parathyroid structure. The case reports of tumors and striking hyperplasias have been collected from time to time. Among the many interesting reviews should be mentioned those of A. Kocher,²⁵ Bérard and Alamartine,²⁶ Harbitz²⁷ and especially the report of Hoffheinz,²⁸ who discussed all of the cases which he could find from 1900 (De Santi's case) to 1925. He was able to collect 45 cases in which parathyroid tumor or hyperplasia was certain and 15 others, the details of which were too incomplete to allow certain diagnosis.

In examining the literature, we have found a few cases which Hoffheinz omitted. In addition, several new cases have been reported in

the four years which have elapsed since he published his work. These have been summarized as follows:

Cases of Parathyroid Tumors. *Da Costa*:²⁹ A woman, aged thirty-two years, who had a mass in the neck which started at the age of twenty-three years following tonsillitis. Growth was painless, but attained the size of an orange. It was removed under the impression that it was an adenomatous goiter. The tumor was brownish-yellow and irregular. Sections showed parathyroid tissue. One year following operation a similar mass appeared on the opposite side. This was not removed for fear of tetany. No bone lesions or other accompanying pathologic changes were noted.

Bérard and Alamartine:³⁰ A woman, aged forty-three years, who had a tumor in the region of the left thyroid which had been growing for several months, causing dyspnea. In removing it, it was necessary to traverse 4 or 5 mm. of thyroid tissue. It was nodular and measured 20 by 15 mm. Microscopic examination revealed parathyroid tissue which was considered adenomatous. No mention was made of bone disease or other pathologic changes.

Roffo and Landivar:³¹ A man, aged sixty years, with malignant tumor, arising in the region of the left lobe of the thyroid and metastasizing to the upper mediastinum. Examination following operation and later by autopsy, indicated a parathyroid origin.

Bergstrand:³² A woman, aged fifty-seven years, who died of pneumonia. At autopsy she was found to have, in addition to pneumonia, an arteriosclerotic disease of the kidneys and a parathyroid tumor. Bergstrand found 10 other cases of severe nephritis in which there was hyperplasia of the parathyroids.

Hubbard and Wentworth:³³ A man, aged twenty years, with chronic interstitial nephritis, hydronephrosis, osteitis fibrosa of skull, ribs and vertebrae, with metastatic calcification of unusual degree in auricle, in arteries and about joints, but sparing liver, spleen, lungs, kidneys and stomach. Two parathyroid glands were about 2 cm. in diameter.

Bergstrand:³⁴ A woman, aged twenty-two years, who died suddenly after an unexplained illness. The thymus and two parathyroid glands were greatly enlarged.

Bergstrand:³⁴ A woman, aged fifty-eight years, who died following a hemiplegia. An enlarged thymus and two enlarged parathyroids were found at autopsy.

Fraenkel:³⁵ A case of *ostitis fibrosa generalisata*, with large parathyroid tumor.

Fasiani:³⁶ A woman, aged sixty-five years, who had always had a small mass in the right side of neck. For a short time she had noted a mass in the left side which grew rapidly until it attained the size of an adult fist. It was accompanied by severe pain. An attempt to remove it was unsuccessful, the patient dying on the table. The tumor had the structure of parathyroid tissue, was undoubtedly malignant and had invaded the thyroid gland.

Klemperer:³⁷ A woman, aged forty-nine years, who had a generalized carcinomatosis of bone from a primary tumor of the breast. Left inferior parathyroid measured 30 by 5 by 3 mm., was yellow and dense in consistency. Since the appearance was that of normal parathyroid gland, and the overgrowth was not limited to any one type of cell, it was considered to be a simple hyperplasia. In two areas of the parathyroid there were small nodules of metastasis from the primary tumor.

Looser:³⁸ A woman, aged fifty-one years, whose case was diagnosed *ostitis fibrosa* with cysts and brown tumors. At autopsy a tumor the size of a walnut was found back of the lower pole of the right lobe of the thyroid but separated from it. While it is probable that this was a parathyroid tumor, the description is not sufficiently complete to permit a certain diagnosis.

Dawson and Struthers:³⁹ A man, aged forty-nine years, who had a typical picture of *ostitis fibrosa cystica* with pathologic fractures. At autopsy five parathyroid glands were found. Four were normal or slightly enlarged; the fifth was the size of a walnut. Microscopically the appearance was that of a parathyroid adenoma.

Ferrero and Sacerdote:⁴⁰ A woman, aged sixty-five years, who had had a tumor in her neck for fourteen years. For three years she had noticed a tumor of the forehead. Operation on frontal region revealed an invasive malignant tumor which had the structure of parathyroid tissue and was diagnosed as a

malignant parathyroid tumor by the authors. No examination of the original tumor in the neck was reported. No changes in bones were found.

*Kerl:*⁴¹ A woman, aged fifty-nine years, who, following childbirth at twenty-eight years, had developed symptoms of osteomalacia which was recognized and studied intermittently during the interval. At autopsy osteomalacia was apparent, but no cysts or tumors of the bones were described. All four parathyroids were said to be enlarged, measuring about 0.8 by 1 cm.

*Kerl:*⁴¹ A woman, aged sixty-three years, who died of a cancer of the cystic duct. Twelve years before she had been diagnosed as a case of osteomalacia. At autopsy metastases from the primary tumor were found in the liver, the ovaries, the mesenteric lymph nodes and in the abdominal cavity. None were found in the bones. Parathyroids measured 10 by 6 by 4, 12 by 7 by 4, 25 by 5 by 3 and 11 by 5 by 4 mm. The condition of the bones was diagnosed as osteoporosis.

*Gödl:*⁴² A woman, aged forty-two years, who was examined at autopsy following an operation for giant-cell sarcoma of the tibia. No other bone lesions were found. There were two tumors of the parathyroid, one 10 by 2 cm. and the other 5.4 cm. in diameter.

*Nagelsbach:*⁴³ A man, aged twenty-five years, with a tumor of the left upper parathyroid the size of a walnut, reported as pure hypertrophy. Accompanying this there was an extensive fibrous change of the entire skeleton.

*Pencke:*⁴⁴ A man, aged thirty-eight years, who died of a chronic nephritis. At autopsy contracted kidneys and metastatic calcification was found in the muscle of the left heart, in the smaller arteries, in the thyroid, kidneys and spleen. The great vessels remained free. There was also calcification in the apices of the lungs, in the skin and in the walls of the parathyroid tumor. Concretions were present in no other organs of internal secretion. The bones showed a picture of *ostitis fibrosa*.

*Pencke:*⁴⁴ A woman, aged fifty-nine years, who died of *erysipelas*. Diagnosed as *ostitis fibrosa*. The right lower parathyroid weighed 5 gm. The left lower, while not enlarged, showed the areas of proliferation described by Erdheim.

*Perreira and Castro-Freire:*⁴⁵ A young man, diagnosed as generalized fibrous *ostitis*, who had symptoms from the age of four years; a traumatic fracture at nine years; well-marked osteomalacia with cyst formation at sixteen years; death at eighteen years. At autopsy a parathyroid tumor was found. This was considered hyperplastic by the authors.

*Herxheimer:*⁴⁶ A man, aged thirty-two years, who showed at autopsy a mitral stenosis with calcium deposits in the heart muscle, in the aorta, the kidneys, lungs and wall of the spleen, but no calcification in the gastric mucosa. He had no pathologic changes in the bones. Three parathyroids were found. One was adenomatous and as large as a cherry.

Mandl:^{47,48} A man, aged thirty-eight years, with severe generalized *ostitis fibrosa cystica*. At operation a parathyroid tumor measuring 25 by 15 by 12 mm. was found.

*Guy:*⁴⁹ A woman, aged twenty-nine years, who had had for six years a tumor of the neck in the region of the left lobe of the thyroid. The swelling was removed by operation. It measured 8 by 6 by 4 cm. and was diagnosed adenoma of the parathyroid. Ten months later the patient returned with three nodular swellings of the neck, interpreted by the author as compensatory hyperplasia of the remaining parathyroids. No bone changes were mentioned.

*Allesandri:*⁵⁰ A man, aged fifty-one years, with a tumor of the right humerus which followed an injury. Although there was no tumor in the region of the thyroid, the diagnosis of mixed thyroid and parathyroid adenocarcinoma was made from microscopical diagnosis of the tumor of the arm.

*Gold:*⁵¹ A woman, aged fifty-four years, with generalized *ostitis fibrosa cystica*. At operation a parathyroid tumor measuring 25 by 16 mm. was found.

*Beck:*⁵² A woman, aged forty-one years, diagnosed *osteodystrophia generalisata*, apparently typical of generalized *ostitis fibrosa cystica*. At operation two parathyroid tumors, one the size of a soft-shelled almond and the other the size of a coffee bean, were removed. The patient died of tetany.

*Wilder:*⁵³ A woman, aged thirty-two years, who had typical *ostitis fibrosa*. At operation a parathyroid tumor was removed.

Boyd, Milgram and Stearns:^{54,55} A boy, aged ten years, with evidence of softening of the bones, diagnosed after clinical and Roentgen ray examinations

as generalized osteitis fibrosa. Operation revealed an adenoma of the left lower parathyroid.

*Snapper:*⁵⁶ A man, aged fifty-six years, with osteitis fibrosa cystica and an unusual degree of decalcification of bones. A parathyroid tumor was removed at operation.

Adding these 29 cases to those collected by Hoffheinz, a total of 74 examples of pathologically enlarged parathyroid glands may be considered. These include both malignant and benign tumors, as well as enlargements due to simple hyperplasia. Authentic malignant growths of the parathyroid glands are extremely rare, and it is a matter of interest that none of them has been associated with evidence of functional derangement of the parathyroids or with important conditions in the bones or elsewhere. The criteria for differentiating benign tumors from simple hyperplasia are ill defined. In some of the cases in which one is most tempted to diagnose tumors, there may be multiple growths. Guy's⁴⁹ patient returned ten months after operation with similar tumors in the region of the other parathyroid glands. Gödl's⁴² patient had two large but quite separate parathyroid tumors. Such findings could be explained more simply on the basis of hyperplasia than of true tumor formation. All but about 17 of the parathyroid enlargements must, therefore, be considered to have resulted from hyperplasia.

Conditions Associated with Enlargement of the Parathyroid. Of the clinical conditions which have been reported in association with enlargement of the parathyroids, some appear to be incidental while others are found so frequently that they must be regarded as a possible cause or a possible result of the parathyroid changes.

Erdheim¹² described a case of parathyroid tumor in which acromegaly was present and in which a pituitary tumor was found at autopsy. Fine and Brown⁵⁷ mention a patient seen in Cushing's Clinic with acromegaly. In the third case of Molineus⁵⁸ there was found at autopsy a large tumor of the hypophysis with pressure atrophy of the surrounding bones. There was exophthalmos but no signs of acromegaly or any other functional disturbances of the pituitary gland were apparent.

In Herxheimer's⁴⁶ case the parathyroid enlargement was associated with mitral stenosis and cardiac decompensation. In one of Harbitz's²⁷ patients there was a generalized ichthyosis.

Possibly more significant are the cases associated with nephritis.

MacCallum's⁵⁹ patient, a young man, died in uremia following a nephritis, the symptoms of which had been apparent for several years. A parathyroid tumor was found at autopsy. He studied 2 other cases of advanced chronic nephritis and found in 1 abundant mitoses in the cells of the parathyroids. Bergstrand³² saw 1 case of nephritis in which there was a small parathyroid tumor and 10 others in which the parathyroids were enlarged. Hubbard and Wentworth's³³ case of osteitis fibrosa had an advanced interstitial nephritis. Box and de Wesselow⁶⁰ saw a patient with nephritis in whom the serum calcium was elevated to 14.7 to 20.1 mg., a finding which was interpreted as possibly indicative of abnormal parathyroid function.

Still more striking and important is the association of many diseases of bones with hyperplasia or tumors of the parathyroid glands. In 45 cases collected by Hoffheinz, 27 had some disease of bone, while in the 29 patients whose records we have assembled, no less than 18 were so afflicted. Combining these figures, it appears that 60 per cent of

all cases of parathyroid enlargement have had evident bone lesions. If we exclude from the total number the 17 cases which may be considered either malignant or benign tumors, the association of osseous changes with parathyroid hyperplasia becomes even more impressive.

Of the 45 patients with diseased bones, 9 were diagnosed osteomalacia by the authors, 2 were thought to have rickets, 1 had general metastasis to bone from a mammary cancer; 1 had a localized giant-cell tumor of the tibia; 32 suffered from the generalized form of *ostitis fibrosa cystica*. In addition to these case reports, one should mention several more inclusive studies of the parathyroid glands in rickets and osteomalacia. Ritter⁶¹ and, later, Pappenheimer and Minot⁶² studied groups of children with rickets and compared them with children dying from other conditions. They found that the tendency to hyperplasia was general in rickets, thus establishing in children a fact which Erdheim¹⁴ has already demonstrated in animals. In some instances the enlargement was slight, while in others the parathyroids were more than double the normal size. Thomas,⁶³ who studied the parathyroids in osteomalacia showed that in 6 out of 30 cases there was definite enlargement.

These observations leave no doubt that hyperplasia of parathyroid tissue is associated with many types of bone disease. Clinically the most frequent as well as the most striking association is with the generalized form of *ostitis fibrosa cystica*.

Generalized Ostitis Fibrosa Cystica (von Recklinghausen's Disease). In 1891 von Recklinghausen⁶⁴ published, in the volume commemorating Virchow's seventy-first birthday, a paper entitled "*Ostitis, Osteomalacia and Osteoplastic Carcinomatosis*." He also referred to a case reported several years earlier by Virchow.⁶⁵ Although there may be some doubt as to the proper classification of Virchow's case, there can be little question that the patient described by Hirschberg,⁶⁶ two years before the appearance of von Recklinghausen's paper, suffered from the generalized form of *ostitis fibrosa cystica*. Since that time occasional and scattered references to the disease have appeared in the literature. About 50 well-studied cases have accumulated and extensive reviews have been written by Dawson and Struthers,³⁹ Stenholm⁶⁷ and Mandl.⁴⁸

The disease is more frequent in women and occurs usually in adult life. The age, however, is more variable. The cases of von Haberer,⁶⁹ Lissauer⁷⁰ and Bergmann⁷¹ started in childhood, while Hart's⁷² patient was an old man.

The cysts and tumors affect the long bones most frequently, but the jaw, pelvis and even the bones of the head (von Haberer⁶⁹) may be involved. The swellings usually are not large, and when covered, as in the thigh, with heavy musculature, may not be recognized until a pathologic fracture calls attention to them. Fractures are extremely common, occurring most often in the femur and humerus. Pain accompanies the fractures, but in some cases seems to be an independent feature and, as in von Recklinghausen's original case, occurs in bones which are not known to be subject to fractures or injury.

Microscopically the swellings of the bones show hemorrhages which in some cases seem to dominate the picture. Barrie⁷³ designated his case as one of "*hemorrhagic osteomyelitis*." There is much fibrosis, and in many instances hemorrhage has been an obtrusive feature. Scattered in the fibrous tissue, a great number of giant cells may be found. The structure cannot be differentiated from that of the so-called giant-cell sarcoma of the type found in epulis.

The bone pathology is by no means limited to the cysts and tumors. In most cases there is a localized or general decalcification. This may be the predominant feature, as in Hart's case, which was called "osteomalacia with cysts and tumors." The frequency of the association may be judged from Morton's⁷⁴ review, where it is found that of 63 cases, 42 had either local or general softening and rarefaction of bone. Under these circumstances it might be thought and, indeed, has been stated, that *ostitis fibrosa cystica* is only a form of osteomalacia. Although the definition of osteomalacia is confused, the state most often so designated is associated with childbirth. Except during famine, it has occurred almost entirely in women. *Ostitis fibrosa cystica*, on the other hand, is not uncommon in men, and has no striking association with childbirth. Von Haberer⁷⁵ and Schmorl⁷⁶ consider that the softening of the bones in von Recklinghausen's disease has no relation either to puerperal osteomalacia on the one hand or to rickets on the other.

Von Recklinghausen did not recognize the parathyroid disturbance of the disease, and it was not until 1904 that Askanazy⁷⁷ found a parathyroid tumor in a woman with a disease which he called *ostitis deformans* without osteoid tissue, but which from the description may be considered *ostitis fibrosa*. Schmorl⁷⁸ reported a case of parathyroid hyperplasia in association with "osteomalacia and melanotic tumors," which was probably descriptive of the hemorrhagic cysts of von Recklinghausen's disease. Great impetus was given to the search by the excellent report of Molineus,⁵⁸ who saw 3 cases of typical generalized *ostitis fibrosa*, in all of which he found parathyroid tumors.

As has been stated, 32 cases have been found in which the two conditions have been associated. These, of course, do not include all of the cases of *ostitis fibrosa cystica*. In many of the earlier cases there was no examination of the parathyroids. This applies also to the more recent reports of Martland,⁷⁹ Crile,⁸⁰ Hartung⁸¹ and Young and Cooperman.⁸² But while in these instances the lack of association may be ascribed to failure to look for parathyroid change, there are some cases in the literature in which after meticulous examination no pathologic changes could be found. Stenholm⁶⁷ found 9 examples of typical and at times serious *ostitis fibrosa*, in none of which was there any evidence of pathologic change in the parathyroids. Because of this, the opinion has been expressed that while *ostitis fibrosa cystica* is frequently associated with parathyroid hyperplasia, it is not dependent upon it. Admitting this possibility, it must, nevertheless, be remembered that the recognition of parathyroid tissue is difficult, that it has a wide distribution from the thyroid cartilage to the areolar tissue of the pericardium, and that it may be embedded in the thymus, in the thyroid or even in the tongue. It is also conceivable that tissue which anatomically appears normal may have an increased or changed functional capacity. This possibility is generally recognized in the pathology of other glands of internal secretion.

Although anatomically the association of *ostitis fibrosa* and parathyroid disease had been recognized for twenty years, it was not until 1926 that Mandl⁴⁸ removed a parathyroid tumor by operation. It is significant and important in considering other cases which have been examined only by clinical means that he was unable to find any evidence of enlargement by palpation of the neck. The excised tumor,

however, measured 25 by 15 by 12 mm. Following the operation, there was a marked clinical improvement. The pains in the bones which had been excruciating before the removal of the tumor almost entirely disappeared. There was a gain in weight and increase in muscular power. Roentgen ray pictures showed slight but definite increase in the density of bones in which there had been previous decalcification.

Following Mandl's experiment, a number of similar cases have been subjected to operation for removal of parathyroid tumors.

The patients of Gold,⁵¹ of Wilder⁵³ and of Boyd, Milgram and Stearns⁵⁵ were so greatly improved by the operation as to suggest complete arrest of the progress of the disease. Beck,⁵² however, was not so fortunate, his patient dying of severe tetany twenty days after operation. Of the greatest significance is the case of Du Bois and Aub.⁸³ Operation was performed by Richardson⁸⁴ in the hope of discovering a parathyroid tumor. A most careful and painstaking search over the surface of both lobes of the thyroid revealed no abnormal growth. The removal of two normal-sized and microscopically normal parathyroid glands resulted, however, in great clinical improvement. Indeed, a completely bed-ridden invalid suffering from frequent pathologic fractures was enabled to leave his bed and carry on a useful occupation. This case, besides having an important bearing on the etiologic conceptions of the disease, substantiates the possibility already mentioned, that some of the cases of *ostitis fibrosa cystica* in which no parathyroid lesions were found may have had functional parathyroid derangement not discoverable by the method of examination. Of interest in this connection are the cases of Bauer,^{85,86} Hohlbaum⁸⁷ and Strada,⁸⁸ which are mentioned by Hoffheinz but not included in his list of parathyroid tumors because, while the parathyroids were described as hyperplastic, the size was within the limits arbitrarily considered normal.

In addition to the changes in the bones and the association with parathyroid hyperplasia, *ostitis fibrosa* has a number of most interesting features. The calcium metabolism is extraordinarily disturbed.

Jacob and Schrott,⁸⁹ who were the first to investigate calcium relationships in the disease found an abnormally high excretion of calcium which they thought could be remedied by means of administration of calcium lactate. Mandl⁴⁸ found an increased excretion of calcium in the urine which was reduced to one-sixth of the original amount following the operation. Studies by Gold,⁵¹ Wilder,⁵³ Boyd, Milgram and Stearns⁵⁵ have established an abnormal excretion of calcium in the urine as a constant feature of the disease which is remediable by operation.

The calcium content of the serum is greatly increased, as may be seen from the following table:

Author.	Highest calcium content of serum, mg. per cent.
Gold ⁵¹	13.1
Wilder ⁵³	12.8
Boyd, Milgram and Stearns ⁵⁵	17.6
Du Bois and Aub ⁸³	16.5
Snapper ⁵⁶	23.6

Du Bois and Aub,⁸³ and also Boyd and his associates,⁵⁵ have found hypophosphatemia.

Calcium stones have been reported in the kidneys and ureters.

In 1884, seven years before von Recklinghausen's article, Davies-Colley⁹⁰ described a most interesting case of a girl brought up in a cellar, who developed a disease of her bones before the age of nine years. This was characterized by swellings in the jaw, ribs and pelvis, which were doubtfully considered calluses, but which may well have been due to multiple fibrocystic disease. In addition,

there were extensive calculi in the kidneys and ureters. A similar case without bone swellings was described more recently by Dereux.⁹¹ Schönenberger⁹² saw a case of undoubted ostitis fibrosa cystica in a woman with bladder disturbance and incontinence. The papillæ of the kidney showed small calcium infarcts. Gargel⁹³ described a patient who died of uremia and whose kidneys contained sand and stones that had resulted in hydronephrosis and pyelonephritis. Hoffheinz²⁸ found in his patient calcium infarcts as well as a large coral stone in the upper calyx of the right renal pelvis.

Most interesting metastatic calcification has been observed in a number of cases.

Hoffheinz, in addition to the changes in the kidneys, found calcium deposit in the lungs. Dawson and Struthers³⁹ found calcium infiltration of practically every organ in the body. This took the form of fine granules which in some instances became confluent masses. They were laid in the minute fibers of the elastic and connective tissue, in muscle fibers and also in epithelial cells. They were especially marked in the lungs, stomach and kidneys. No calculi were found. One of the most astounding examples of calcium deposit was recently reported by Peneke.⁴⁴ This patient died of chronic nephritis. At autopsy, calcification was found in the left heart, in the smaller arteries, the thyroid, kidneys, spleen, the skin and in the walls of the parathyroid tumor. The patient of Hubbard and Wentworth³³ had, in addition to ostitis fibrosa cystica, a fatal nephritis. The calcium deposits in the tissues were most extensive, but were found in the heart, the arteries and about the joints. The lungs, kidneys and gastric mucosa were spared.

Functional muscular changes have been noted in a number of cases.

Sometimes when violent pain has been a part of the picture, 'stiffness of the muscles has been described. Other cases, however, have shown an unusual flabbiness or weakness of the muscles. Dawson and Struthers studied the muscles of their patient without discovering any significant pathologic change. Hirschberg⁶⁶ and also von Recklinghausen⁶⁴ mentioned the wasting of muscles which admittedly may have been associated with disuse following injury. Hartung's⁸¹ patient, however, had been diagnosed as a tabetic, although the reflexes were present. Barrie's⁷³ patient had persistent muscular weakness, much worse in winter. Four years before Barrie observed him he had been diagnosed amyotrophic lateral sclerosis. The case observed by Du Bois and Aub⁸³ showed muscular weakness. Electrical tests showed greatly diminished response to stimulation.

This discussion of generalized ostitis fibrosa cystica has not been concerned with a much more common condition designated in the literature as localized ostitis fibrosa cystica, solitary bone cyst or von Recklinghausen's disease. This occurs usually as a single cystic lesion in one bone and most often the femur, humerus or tibia. It is wont to affect young people below the age of twenty years and, although often extremely deforming, is accompanied by no deterioration of health. Pathologically the bone lesion cannot be distinguished from the cysts which have been described in generalized ostitis fibrosa. The relationship of these solitary cysts with giant-cell tumor on the one hand and with generalized ostitis fibrosa on the other has been much discussed and with little agreement. Reference may be made to the recent study of Geschickter and Copeland⁶⁸ on ostitis fibrosa and giant-cell tumor and to the article by Mandl,⁴⁸ who summarizes the evidence of the relationship between the localized and generalized form of ostitis fibrosa.

It is remarkable that, although the case reports of solitary cyst and of single benign giant-cell tumor have been much more numerous than

those of generalized von Recklinghausen's disease, we have been able to find only one, the case of Gödl,⁴² in which there was an associated parathyroid enlargement.

Clinical Observations. A patient showing many of the features characteristic of *ostitis fibrosa cystica* has been observed by us during the past three years. Although her history was presented briefly in a previous publication,⁹⁴ her case is included in the present discussion in order that more complete data with pictures and exhibits may be presented and that the progress of the patient may be reported.

Case Reports. CASE I.—A woman, aged fifty-six years, entered Barnes Hospital, February 9, 1927, because of complete inability to walk, frequency of urination and a swelling of the right forefinger. She had been strong and healthy during her childhood. She married at the age of twenty-two years, but had never become pregnant. She lived with her husband on a small farm, where she worked hard. Some time in her girlhood she conceived a dislike for milk. She had other strong dislikes for food which finally led her to adopt a diet which was extremely ill-balanced. She was well, however, until the age of thirty-eight years, at which time she began to have frequency of urination and was told by her physician that she had an "inflammation of the bladder." For ten days she was in bed because of this disorder. The symptoms gradually cleared up and she remained well for nine years, until the age of forty-seven years, when pain and frequency of urination returned. After six months' treatment her physician told her that she had fibroids and that an operation was necessary. A hysterectomy and a partial oöphorectomy were performed. Following this operation she was never well. The urinary symptoms continued and she began to experience difficulty in walking, at first attributed to flatfoot, but later becoming so bad that she could get about only by supporting herself with her arms. She later noticed an increasing difficulty in lifting her feet from the floor. In February, 1926, from a rather trifling injury she fractured the right clavicle, which healed slowly.

In September, 1926, she injured the right index finger when the leaves of a table closed on it. A roentgenogram was taken of this finger and a diagnosis of syphilis was made by the physician. This alarmed the patient so much that she entered the hospital.

The examination revealed a remarkable degree of muscular hypotonia, most marked in the lower extremities. This seemed to apply both to the joints and to the muscles. The patient was able to go to sleep with her head on her ankles or with both ankles tucked under her head. She had a marked kyphosis; she was unable to walk and could not support herself. Electrical tests of the muscles showed little response to the faradic current. There was a fusiform swelling on the first phalanx of the right forefinger and a similar swelling on the right clavicle. A Roentgenogram of the bones of the skull and other parts showed irregular areas of rarefaction. The urine showed signs of moderate pyelitis. Flat plates of the kidneys revealed large collections of stones in the pelvis. The right forefinger was removed. Examination by Dr. I. Y. Olch revealed a giant-cell tumor of the epulis type. Biopsy of the swelling on the clavicle showed normal callus formation.

After having been treated for her urinary symptoms for some weeks, the patient was sent home with the diagnosis of giant-cell sarcoma, bilateral nephrolithiasis and an unexplained hypotonia of muscles and joints.

She returned in February, 1928. She had been in an automobile accident and had fractured the left humerus. She had had a tooth removed from the upper jaw, and a tumor had formed in the maxilla. A biopsy of the ulnar swelling was suggestive of a benign giant-cell sarcoma, exactly similar to that removed from the right forefinger. No biopsy was obtained on the tumor of the jaw. It had the appearance of a cystic expansion of the maxilla. The teeth were loosened.

Roentgen rays of the skull and pelvis showed a greatly increased rarefaction. At the time of the first admission a punched-out area of rarefaction had been seen in the iliac bone. During the interval this had more than trebled in size. The

skull also showed the effects of a progressive decalcification. The legs which had previously been slightly bowed were definitely more deformed. An interesting change in the thumb which offered striking evidence of the softness of the bones occurred under observation in the hospital. Shortly after she came to As she was given occupational therapy which she undertook enthusiastically. As a part of this work, she had to press down with her thumb on each row of reeds before the next row was applied. This pressure resulted in deformity and bending of the terminal phalanx.

Unfortunately, calcium studies had not been made during the first admission. Examination of the blood now showed a calcium content of 16 mg. and a phosphate content of 1.4 mg. Repeated analyses under a variety of conditions gave a range of values from 12.4 to 16.6 for serum calcium and from 1.4 to 6 for phosphate.* Extensive metabolic studies revealed a constant negative calcium balance, with a loss of calcium in the urine which became greater as the calcium in the diet was increased.†

We were impressed with the similarity between the condition of this patient and that which had recently been produced by overdosage with parathyroid hormone. We were also stimulated by the reports of Mandl and Gold and by personal communication with Du Bois and Aub, whose case had been studied two years before. A reexamination was made of the thyroid region without the discovery of a tumor. After repeated examination, however, a globular mass about the size of a small walnut was found embedded in the left lobe of the thyroid. Ordinarily, this rested beneath the clavicle and could be felt only when the patient swallowed.

Operation was performed by Dr. I. Y. Olch and a parathyroid tumor was removed together with a small portion of the left lobe of the thyroid. The tumor measured about 3 cm. in diameter. The central portion consisted of an irregular cyst which was surrounded by yellowish tissue. Microscopic sections revealed unmistakable parathyroid tissue which did not deviate significantly from the normal appearance of the parathyroid gland.

About two days after the operation the patient began to complain of slight tingling and numbness of the hands and a tightness and twitching of the corners of the mouth. At this time her serum calcium was still above the normal level. The following table gives in brief a record of the extraordinary picture which developed during the days following the removal of the parathyroid tumor. In spite of large, even heroic doses of parathormone and of great amounts of calcium by mouth, the condition of the patient became steadily worse, until it appeared that she would die of tetany. Her life was apparently saved by the use of calcium chlorid intravenously. Following this period of acute symptoms, the patient gradually improved. It was not possible, however, to discontinue parathormone or the large doses of calcium.

During the first ten months following her operation she retained more than 300 gm. of calcium and was at all times in positive calcium balance. She developed no more tumors of the bones. Both the ulnar and the maxillary tumors decreased in size. The teeth which had been loose became tight in their sockets. Her muscular strength and tone improved rapidly for a period and then remained almost stationary and far below normal. Electrical tests showed the muscles to be more sensitive to the faradic current than they had been before operation. Frequent Roentgen ray pictures indicated a definite increase in the calcification of bones but not as great as might have been expected from the amount of calcium which she stored.

For several months she was watched in the hope that her increasing strength might enable her to bear her weight and to walk. Since this did not occur she was given massage, passive motion and physical reeducation. After weeks of this treatment she was able to walk for some distance holding onto a stretcher for support.

Her urinary symptoms showed no improvement; pain and frequency seemed to increase until they became almost unbearable. Examinations by Dr. D. K. Rose revealed that her bladder was of unusually small size with thick walls which went into spasm with slight irritation.

* This higher value was observed during a period of high phosphate feeding.

† The details of the metabolic studies on this and the following cases are being published in a separate report.²⁵



FIG. 1.—Photograph of Case I, showing tumefaction of left maxilla, extreme flabbiness of muscles and abnormal mobility of joints.

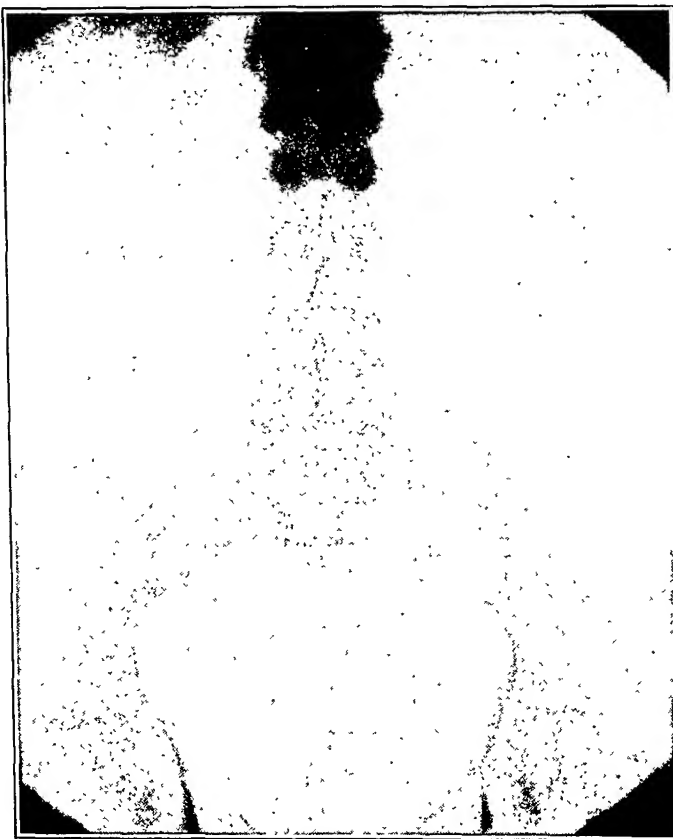


FIG. 2.—Roentgen ray of kidney region of Case I, showing bilateral nephrolithiasis.

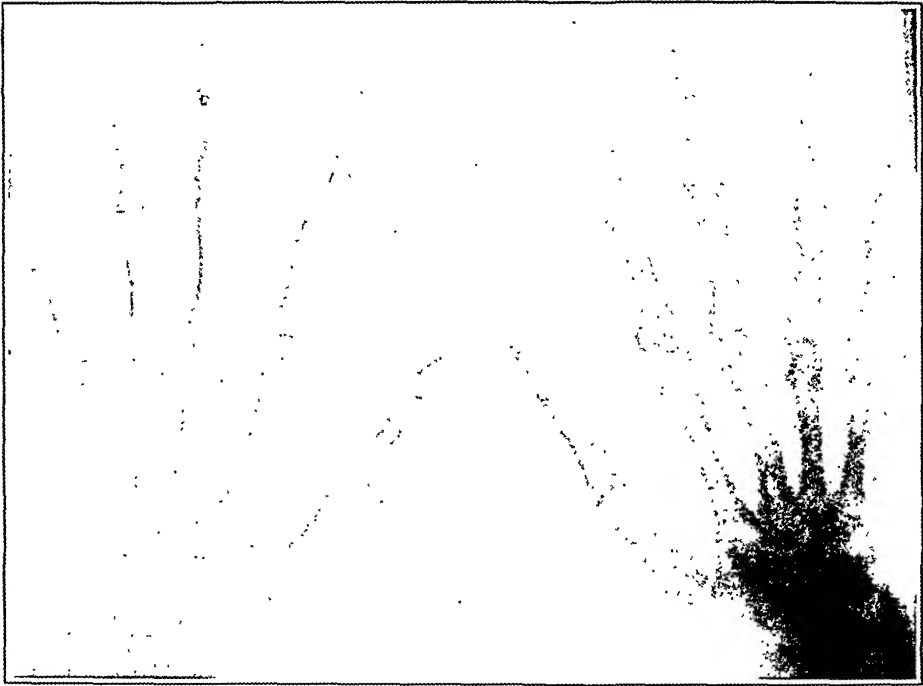


FIG. 3.—Hands of Case I, showing irregularity of the outlines of phalanges and the giant-cell tumor of the first phalanx on the right hand.



FIG. 4.—Longitudinal section of amputated first phalanx in Case I, showing extent and character of giant-cell tumor.

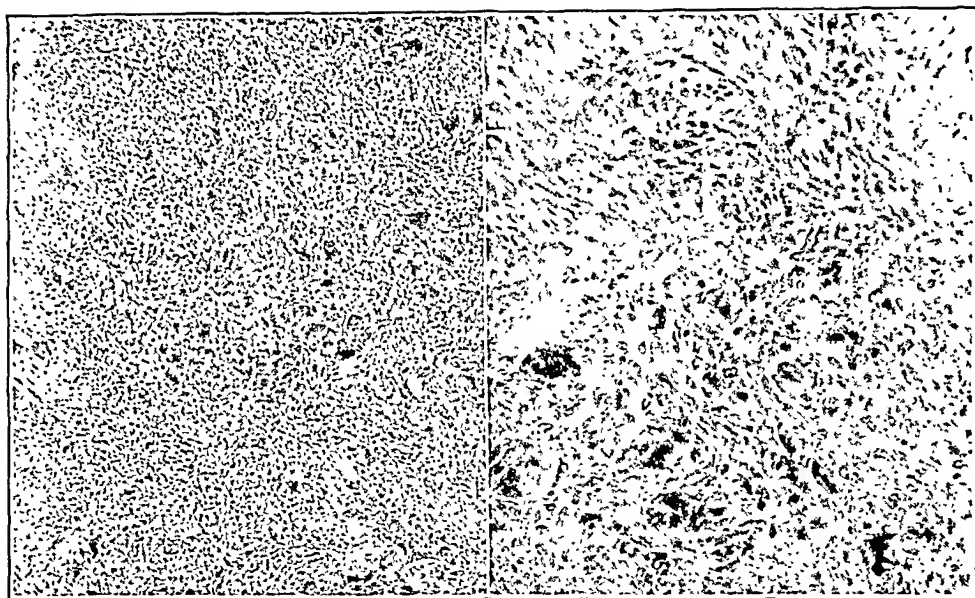


FIG. 5.—Microscopic appearance of giant-cell tumor of Case I. *A*, low power; *B*, high power.



FIG. 6.—Microscopic appearance of parathyroid tumor of Case I.

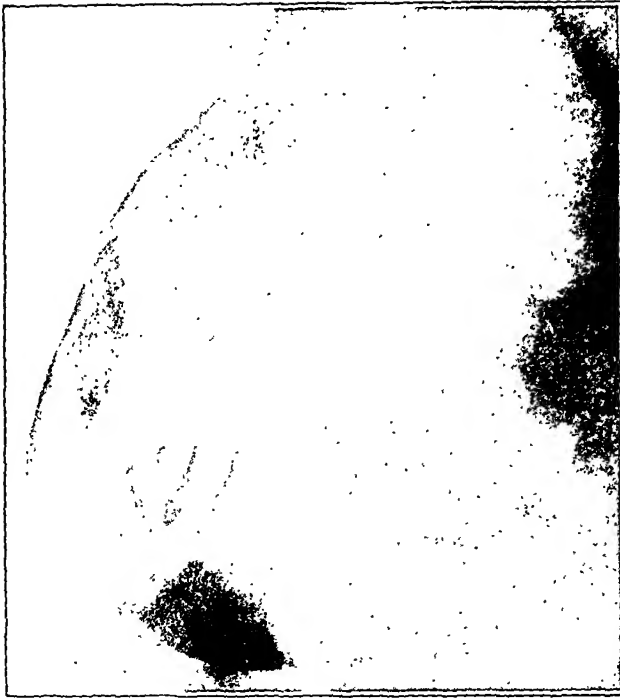


FIG. 7.—View of left mandible and left maxilla, showing circular area of rarefaction at the roots of the left lower molars; the large area of rarefaction at the symphysis and another view of the tumor of the maxilla.

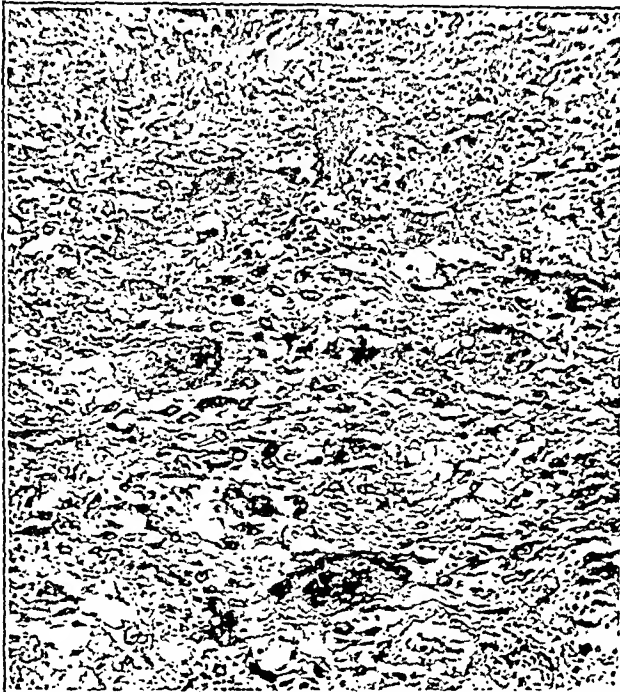


FIG. 8.—High-power view of the giant-cell tumor of Case II.



FIG. 9.—Spine of Case III, showing moth-eaten appearance of lower lumbar vertebræ and sacrum. To be compared with clear-cut outline of upper lumbar vertebræ.



FIG. 10.—Metastatic calcification of the alveolar walls in the lungs of Case III.

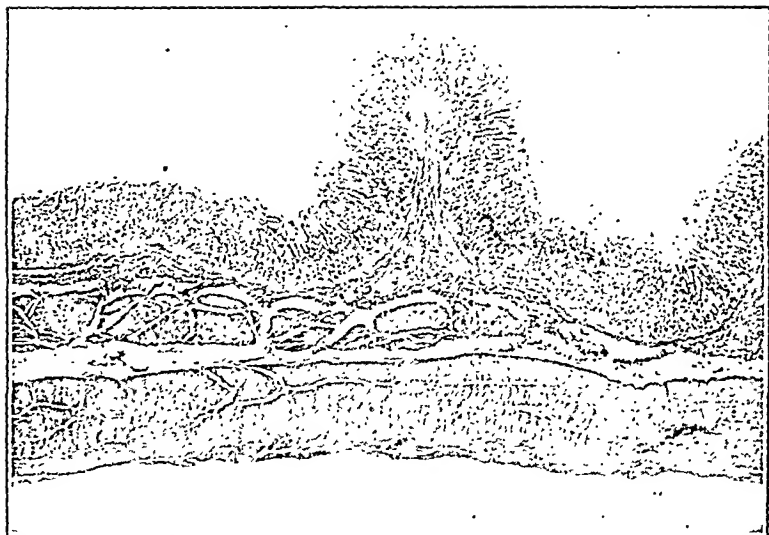


FIG. 11.—Metastatic calcification in the gastric mucosa of Case III, shown by line of dark-staining material in the lower portion of the glands.



FIG. 12.—Metastatic calcification of kidney in Case III, showing calcium within the tubules and in the tissues surrounding them. The large patch of calcium in the right lower portion of the figure has completely replaced the tubule.

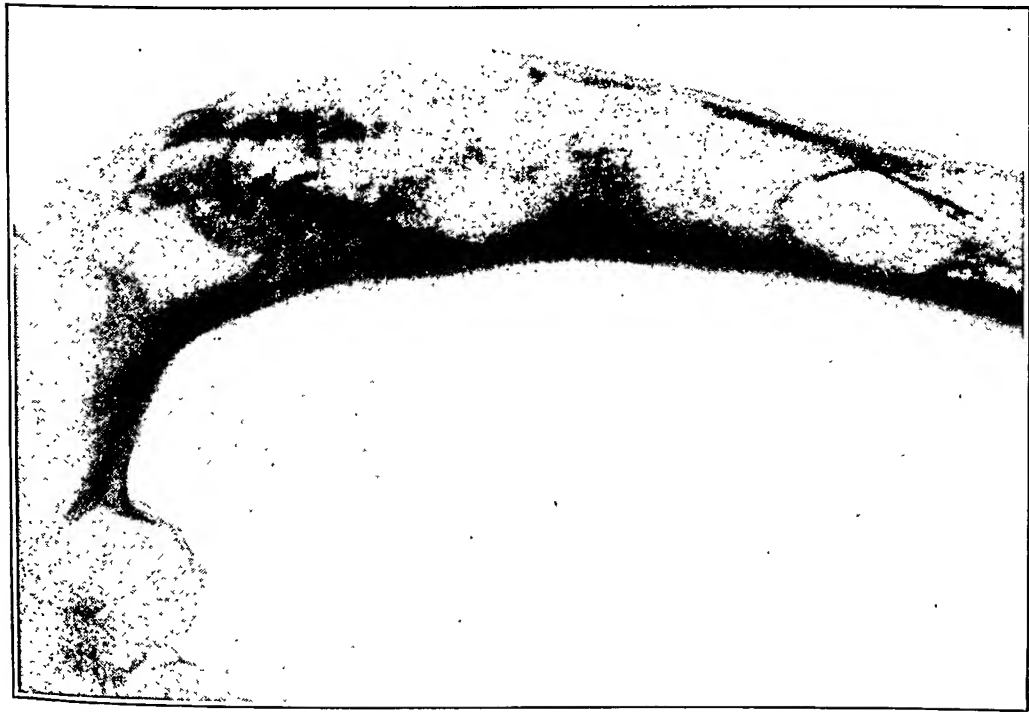


FIG. 13.—Femur of Case IV, showing multiple cysts.

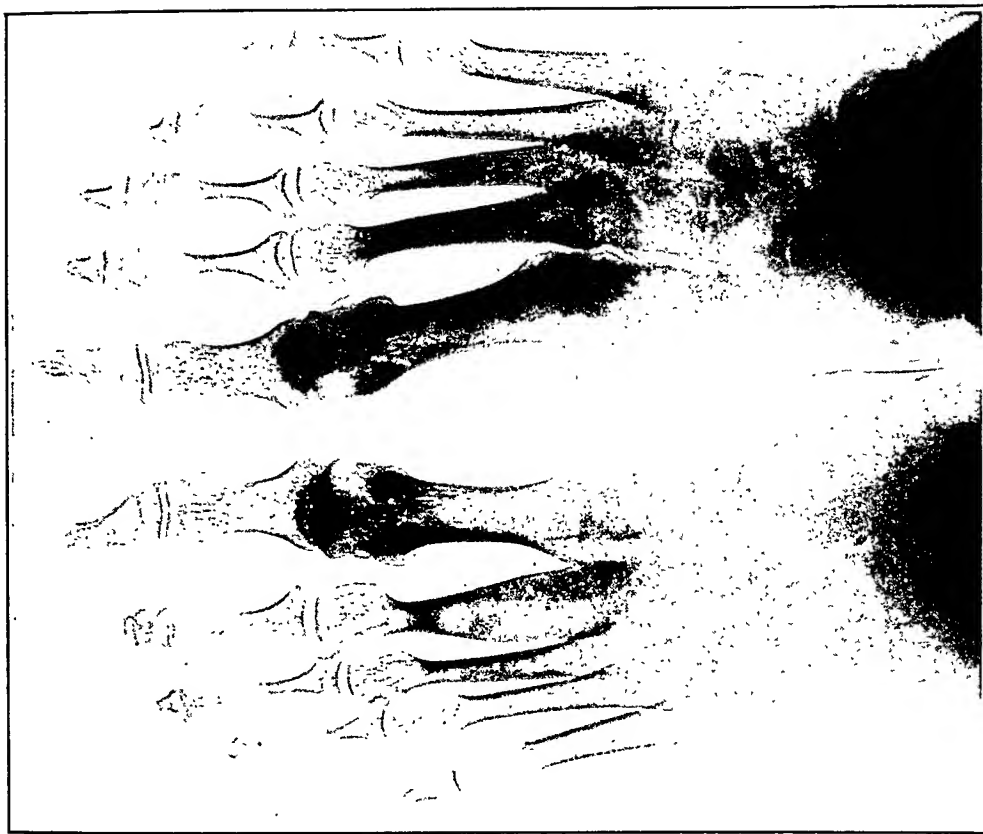


FIG. 14.—Feet of Case IV, showing enlargement of second metatarsal of left foot.

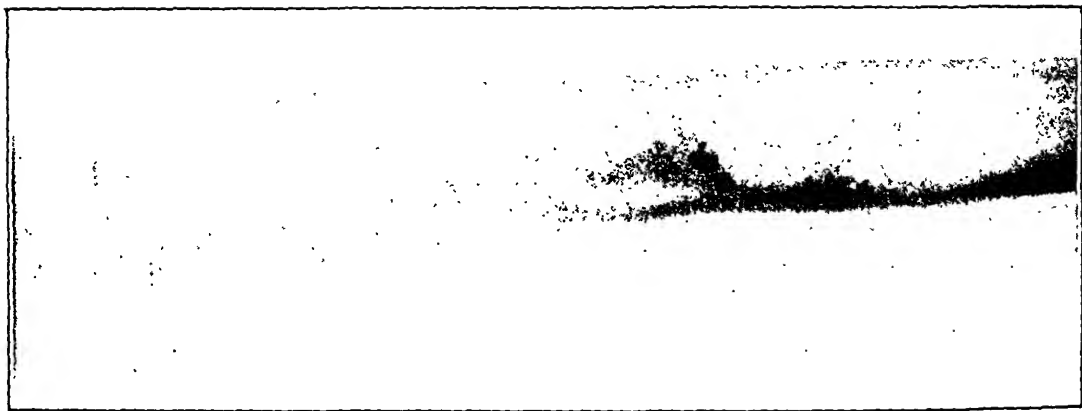


FIG. 16.—Tibia of Case V, showing cyst.

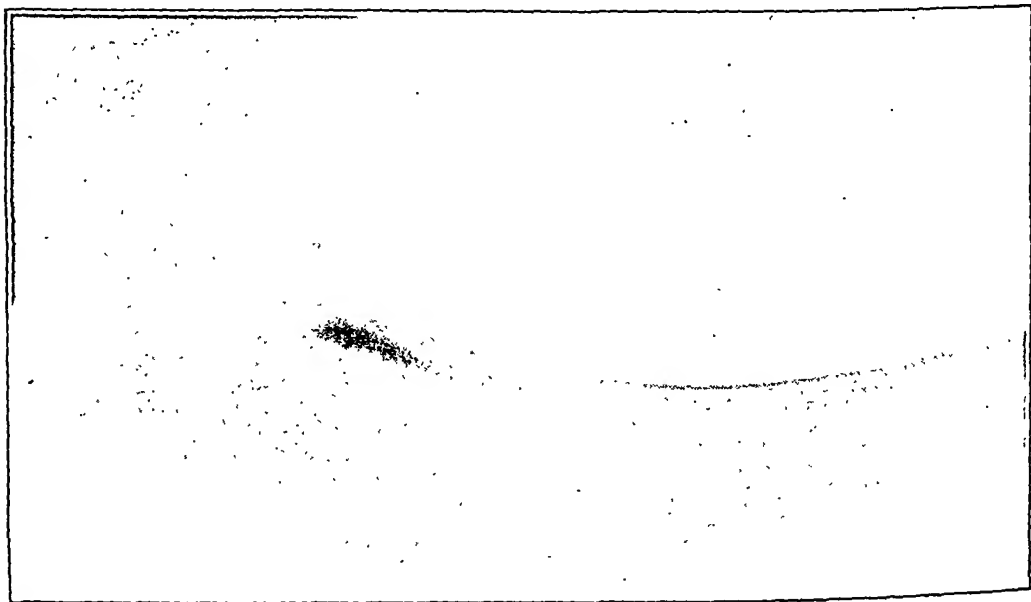


FIG. 15.—Femur of Case V, showing cysts.

Day after operation.	Calcium in serum, mg. per cent.	Phosphorus in serum, mg. per cent.	Treatment.		Remarks concerning symptoms and treatment.
			Calcium lactate, gm.	Parathormone, units.	
Before . . .	16.4	1.3			
Second . . .	12.9	3.0			
Fourth . . .	11.3	2.2	Beginning signs of tetany.
Seventh . . .	10.8	5.2	Depression, vomiting, twitching of face, positive Chvostek; pains in legs.
Ninth . . .	7.4	11.2	Increase in symptoms with spasm of larynx; nonprotein N., 33 mg. per cent.
Tenth . . .	7.5	10.3	6		
Eleventh	12	...	Pains in muscles more severe; spontaneous muscle contractions.
Twelfth . . .	7.5	3.0	10		
Fourteenth	6	25	
Fifteenth . . .	6.5	3.4	18	35	Rapidly growing worse; signs of tetany less evident.
Sixteenth . . .	4.1	3.2	12	75	Blood sugar, 135 mg. per cent
Seventeenth	18	50	Conditions grave; irrational.
Eighteenth . . .	5.0	3.0	18	200	No objective signs of tetany; conditions grave.
Nineteenth . . .	5.1	3.1	18	125	Nonprotein N., 31 mg. per cent
Twentieth . . .	5.4	...	40	250	Condition about same; no signs of tetany; slight edema of ankles; B.P., 110/78.
Twenty-first . . .	5.5	...	22	100	1.7 gm. calcium chlorid intravenously.
Twenty-second . . .	7.5	3.7	18	50	Remarkable improvement overnight; 2 gm. calcium chlorid intravenously.

In July, 1929, she suddenly lost the power to move her legs. Deep reflexes had never been obtained and were not found after the paralysis. There was loss of superficial and deep sensibility and of the position sense. The muscles again became extremely flaccid. No sensory level, however, was discovered. Examination by Dr. S. I. Schwab failed to reveal a definite level of the lesion.

Roentgen ray of the spine showed, as before, a marked kyphosis. It was believed, therefore, that the cord had been subjected to pressure because of the abnormal position of the vertebræ. The use of a fracture board and some protection against weight bearing resulted in return of motion and sensation. Since this accident, however, she has not attempted to walk. She has lost some weight and there has been slight deterioration of her general condition. Recently she has shown an increasing infection of the bladder and renal pelvis with impaired kidney function and nonprotein nitrogen retention of 50 mg.

This is considered to be a case of *ostitis fibrosa cystica* with bone cysts, giant-cell tumors of the epulis type, decalcification and softening of bone. It has the additional but also characteristic features of muscular hypotonia and nephrolithiasis, hypercalcemia, a tendency to excrete calcium in abnormally large amounts in the urine and hypophosphatemia.

Removal of a parathyroid tumor caused severe and almost fatal tetany, produced a hypocalcemia and a strongly positive calcium

balance and hyperphosphatemia. It prevented any advance in the bone disease and resulted in some subjective and objective improvement.

The hypotonia exhibited by this patient is greater than has been previously reported. It seemed to involve the joints quite as much as the muscles. Furthermore, the ability of the patient to do contortionist tricks did not disappear with change in the muscles following operation. The patient gave a history of being unusually limber as a girl, and it is found that two members of her family are able to do modest contortionist stunts. Thus, while the muscular hypotonia and the lack of response to electrical stimulation were definite and striking features, they explain only in part the unusual mobility of the joints.

The development of tetany in this patient deserves special comment. It is by no means an isolated instance. Although Wilder's⁵³ patient did not develop actual tetany, she suffered three days after the operation from numbness and tingling of the fingers and toes which was relieved by calcium administered intravenously. Snapper's⁵⁶ patient had severe tetany with mania, relieved with difficulty by parathormone. Beck's⁵² patient died with symptoms of tetany twenty days after operation. In this case, however, two parathyroid tumors were removed. It is interesting that in our patient the symptoms started while the serum calcium was above the usual normal level. They continued to increase while huge doses of parathormone were being given and while an abundance of calcium was being administered by mouth. At a time when her condition was becoming rapidly worse and hope for her recovery was all but lost, the intravenous injection of a comparatively small amount of calcium chlorid caused a most dramatic improvement. Although it was quite naturally assumed that the calcium taken by mouth had not been absorbed, later analysis showed that this was not true. In the entire period during which the tetany was developing, there was absorption of very large amounts of calcium. One can only conclude that calcium chlorid or the intravenous administration has some unexplained specific effect. This will be discussed in a paper on calcium metabolism in hyperparathyroidism. The successful use of intravenous calcium chlorid is emphasized here only because of its therapeutic importance.

Examination of the tissue removed at operation revealed only one parathyroid gland. Although it was expected that the remaining parathyroid tissue would be more than sufficient for the needs of the patient, acute tetany developed immediately, and now, after many months daily injections of parathormone are needed to prevent its recurrence. It can scarcely be assumed that this loss of parathyroid function is the result of postoperative adhesions or of injury of the blood supply of the remaining parathyroid tissue at the time of operation, since manipulation was limited to the left lobe of the thyroid gland and the right lobe was entirely undisturbed. The explanation is by no means clear. It seems possible that with the growth and hyperfunction of the parathyroid tumor, the remainder of the parathyroid tissue underwent a gradual but finally complete atrophy. It is also conceivable that there was a congenital absence of all but one parathyroid gland. In Erdheim's⁹⁶ first case of parathyroid tumor he found no other parathyroid tissue. Strauch⁹⁷ saw a patient with osteomalacia and

Günther⁹⁸ one with multiple giant-cell tumors, in both of whom a parathyroid tumor but no other parathyroid tissue was found.

- Another possibility may be mentioned. During the state of hyperparathyroidism great amounts of calcium are removed from the bones, presumably because too great an amount of the parathyroid hormone is present in the body. Since with sudden removal of much parathyroid tissue the power of depositing calcium in the bone is restored, it might be assumed that calcium-hungry bones seize so much of the available calcium that other tissues and the blood are depleted and that tetany results. The events in the postoperative course of Snapper's patient furnishes some support for this explanation. The symptoms of tetany which developed shortly after the removal of the parathyroid tumor were extraordinarily severe. Recovery, however, was complete and during subsequent observation the patient exhibited no tendency to return to a state of tetany. In our own patient the explanation is not so completely satisfying. After fourteen months serious symptoms of tetany still develop whenever parathyroid and calcium are omitted in her treatment. The great amount of calcium absorbed during the period should presumably have satisfied any special avidity of the bones. It is fair to state, however, that the amount of parathormone necessary to maintain approximately normal calcium values is now somewhat less than during the first few months after operation.

CASE II.—A farmer, aged thirty-eight years, entered Barnes Hospital, December 12, 1928, on the division of plastic surgery, complaining of a swelling of the jaw. The family history appeared quite unimportant. He had measles, mumps, whooping cough and pneumonia during childhood. He was well and strong until five years before admission, when following abdominal symptoms he was operated upon for gastric ulcer. Three years before admission, following a gastric hemorrhage, a second operation was performed for the same trouble. Thereafter he had little or no return of the gastric symptoms. His teeth had been in poor condition for years without any dental care. There was no history of dietary abnormality. He always liked milk and frequently drank as many as five glasses at a meal. There was nothing in the history suggestive of muscle hypotonia excepting an indefinite story of a short period about one year before admission, when he was "weak in his bones." Following his first abdominal operation he had had some nocturia; otherwise there were no urinary symptoms.

About eight months before the first admission to the hospital he noticed what he called a "gum boil" of the upper jaw on the left side. At no time was it painful. This gradually became larger. Three teeth at the site of the lesion became loose and were extracted by the patient himself with only slight local bleeding. A week before admission he had three severe hemorrhages from the gum.

The patient was well nourished and did not appear ill. His muscles were normally developed and of good tone. The heart, lungs and abdomen appeared normal. The blood pressure was 146 systolic and 80 diastolic. In place of the upper left canine and first and second bicuspid teeth, a tumor was present which extended into the hard palate and anteriorly beyond the alveolar margin. It was firm and not tender.

The urine showed no albumin or casts, no sugar and a varying specific gravity. The blood showed 4,600,000 red blood cells; 80 per cent hemoglobin and 14,500 white blood cells. The Wassermann and Kahn reactions were negative. The phenolsulphonaphthalein excretion was 55 per cent in two hours.

Roentgen ray examination disclosed five tumors of the jaw. Near the one which had been recognized clinically there was an unerupted canine, and it was thought at first that the rarefaction of bone represented a dentigerous cyst. There was a large area of rarefaction extending from the lower incisor teeth to the symphysis menti; another was seen in the region of the right upper canine tooth. Tumors were also seen in both lower molar regions.

At two operations these were all removed by curette and cautery and treated with radium and deep radiation by Roentgen ray. Microscopic examination of the tissues removed at operation showed the tumors to be made up of cellular fibrous-tissue stroma in which there were vast numbers of large giant cells of the type seen in epulis.

About six weeks after the operations on the jaws the calcium and phosphorus content of the serum was studied for the first time. The serum calcium was found to range from 13.3 to 16.7 and serum phosphorus from 1.2 to 2.9 mg. per 100 cc. A more careful examination of the neck revealed a mass apparently about 1 inch in diameter, palpable just above the inner end of the left clavicle. This was elevated and more easily felt when the patient swallowed. The patient was then more completely studied as a case of hyperparathyroidism. There was still no evidence of hypotonicity of the muscles. Faradic stimulation of his muscles, however, required a somewhat stronger current than was needed by several normal persons used as controls. Roentgen ray of the urinary tract showed no evidence of stones. The urine displayed, at times, a slight trace of albumin and occasional casts.

During the interval of six weeks following operation he developed anemia. The blood showed: Red blood cells, 3,960,000; hemoglobin, 50 per cent; white blood cells, 8500; polymorphonuclears, 73 per cent; eosinophils, 1 per cent; lymphocytes, 23 per cent; large mononuclears, 3 per cent. It was felt that this might be the result of an unusually severe general effect of the radium treatment and perhaps to some extent related to the diffuse osteomyelitis of the jaws which had followed the operations.

Roentgen ray of the skull and the long bones of the body showed no other bone tumors and no osteoporosis.

Detailed studies of calcium metabolism showed a definitely negative balance, the excess excretion being chiefly in the urine. The urinary excretion was not greatly increased by a high-calcium intake, nor did this increase the serum calcium.

As there was little doubt as to the diagnosis of hyperparathyroidism, the tumor in the thyroid region was removed by Dr. J. B. Brown on June 18, 1929. It was found to extend beneath the clavicle and to be at least twice as large as was expected from the clinical examination. It was spherical and quite solid. The blood supply appeared to be from the inferior surface of the thyroid. Because of the apprehension caused by the almost fatal tetany which developed in our first patient, it was decided, upon the suggestion of Dr. Isaac Y. Olch, to transplant a small part of the mass into the rectus abdominalis muscle. A piece of a little less than 1 cm. in diameter was planted underneath the anterior sheath of the left rectus muscle. Microscopic examination of the tumor revealed normal parathyroid tissue with no evidence of malignancy.

Twenty hours after the operation the serum calcium had fallen to 10.6 and continued to fall until a minimum of 8.3 was reached on the eighth postoperative day. The serum phosphorus rose slightly to 3.6 mg. per 100 cc. During this time the patient had never experienced any definite tetany. At one time he had a little tingling about the face and in the fingers. Trousseau's and Chvostek's signs could never be elicited. At about the time the serum calcium was lowest he developed a slight diarrhea with some abdominal cramps lasting part of one day; otherwise he continually felt quite well. The calcium excretion in the urine fell promptly after the operation and became almost negligible, but there was little change in the calcium excretion in the stools. The calcium balance became positive, but there was no such marked tendency to store calcium as was noted with the first patient.

On August 12, 1929, two months after his operation, he returned for observation. The serum calcium was 10.5 and the serum phosphate 2.9 mg. per 100 cc. At this time he appeared to be quite well. He had been working hard and gaining weight. The lesions in his mouth had healed and Roentgen ray showed no evidence of any recurrence of the tumors. No mass could be felt under the scar, where a small part of the parathyroid tumor had been transplanted into the rectus muscle.

In this patient the history and the physical state indicate that the disease was of recent origin. The diagnosis of *ostitis fibrosa* must be made upon the occurrence of multiple giant-cell tumors which for some

reason were limited entirely to the upper and lower jaws. No decalcification or osteomalacic change was obvious in the examination of other bones. Clinical hyperparathyroidism was indicated by hypercalcemia and the abnormally high excretion of calcium in the urine. The muscular changes were slight and detectable only by means of electrical tests. The kidneys contained no demonstrable stones.

Following operation the serum calcium fell below the normal level and minor subjective symptoms of tetany developed. The course, however, is in striking contrast to the violent tetany which developed in the first patient. If in these cases an avidity of decalcified bones for calcium is to be regarded as an important factor in the production of postoperative tetany, its absence in this patient might be explained by the comparatively good state of the skeleton as revealed by Roentgen ray. The possibility must also be considered that the parathyroid tissue transplanted to the abdominal wall became sufficiently active to prevent the appearance of tetany.

It was unfortunate that the symptoms of hyperparathyroidism were not discovered earlier. The bone tumors were considered possibly malignant and the operations and subsequent radiation were correspondingly thorough. If hypercalcemia and the other evidence of parathyroid disturbance had been recognized before operation the possibility of malignancy of the tumors in the jaw would have been considered more remote and the effect of parathyroidectomy as a treatment for the bone tumors might have been tried. Although the result of such procedure cannot be predicted, the fact that the bone cysts of Case I decreased in size following parathyroidectomy suggest that considerable improvement might have resulted and that he might possibly have been spared serious and mutilating operations. The case illustrates the necessity of determining the values for serum calcium upon all patients presenting multiple bone tumors.

CASE III.—A married German woman, aged forty-six years, entered Barnes Hospital, June 28, 1929, complaining of weakness, loss of weight, pain in her back. She was a private patient of Dr. J. J. Singer. The family history appeared quite irrelevant. At the age of ten years she had measles, and at fourteen years pneumonia. As a child there were frequent attacks of sore throat. She had occasional headaches. The patient was married at the age of twenty-two years and one year later her first child was born, being delivered by a midwife. Following this the patient did not do well. She failed to gain strength, and remained in rather poor health for the next four years. The symptoms at this time were indefinite, but were not suggestive of osteomalacia. At the age of twenty-eight years she had a second child. The puerperium was uneventful. She remained well until two years before her admission to Barnes Hospital, when she noticed severe and debilitating night sweats. Lassitude gradually became marked and she slowly lost weight. She had complained of an indefinite soreness in the left lumbar region and in the right shoulder. There was moderate nocturia but no other urinary symptoms. She was quite free from any pulmonary symptoms. For ten months prior to admission she had been treated by her local physician with ultraviolet light. This had given her a good tan color but had not increased her strength. She had lost weight from 135 to 90 pounds.

Examination showed a marked emaciation. There was no apparent pain or discomfort. The skin was warm, moist and elastic. A slight pallor of the mucous membranes was evident, but no cyanosis. The thorax showed nothing abnormal except the emaciation and rapid but regular heart. The abdomen was level with the costal margin. The soft edge of the slightly tender liver could be felt extending to the umbilicus. The spleen could not be felt. The

vertebræ were in good alignment and showed no abnormalities. There was no peripheral arteriosclerosis. Blood pressure was 115 systolic and 70 diastolic. There were no deformities or tumors of the long bones. The deep reflexes were hypoaactive. Marked muscular atrophy was evident. The temperature was 39°; respiration, 18.

The urine on admission was alkaline, of varying specific gravity and contained no albumin, sugar or casts. Blood showed: Red blood cells, 3,250,000; hemoglobin, 48 per cent; white blood cells, 6800; 48 per cent polymorphonuclears; 32 per cent lymphocytes; 2 per cent eosinophils; 6 per cent transitionals; 12 per cent large mononuclears. Wassermann, Kahn and Widal reactions were negative. Nonprotein nitrogen was 38 mg. Phenolsulphonethalein, elimination, 51 per cent in two hours. Routine stool examination was negative.

The first part of the patient's course in the hospital was characterized by extreme weakness and emaciation which seemed to result from a remittent fever, ranging each day from normal to as high as 39° C. With these symptoms pulmonary tuberculosis was suspected, but repeated examination and Roentgen rays of the lungs were negative. Pain in the lumbar region and right shoulder and dull aching pains shooting down the legs from the knees to the ankles became more troublesome. There was, for a while, considerable pain and tenderness in the lower abdomen. This together with Roentgen ray findings suggesting a lesion in the cecum seemed to justify a diagnosis of tuberculosis of the cecum. Operation disclosed no abnormalities except the enlarged liver. Fever continued. She occasionally had headaches and vomited now and then. The emaciation was becoming extreme. She complained bitterly of pain in the lower back and left flank. Roentgen ray finally showed definite pin-point rarefaction throughout all the lumbar vertebræ and to a less extent in the pelvis, with rarefaction and a mottled lacy appearance of the bones but without much flattening of the vertebral bodies. Except for the ribs, no lesion of any other bones was demonstrated. There was no obvious osteoporosis of other bones. She was considered to have a neoplastic disease of bone. No Bence-Jones protein was ever found in the urine.

A study of the calcium and phosphorus of the blood was first made on October 5, 1928, when the disease of bone was first evident. The serum calcium was found to be 16 and phosphorus 3.7 mg. per 100 cc. By this time she had developed evidence of a fairly marked kidney insufficiency. Blood nonprotein nitrogen was about 70 mg. and phenolsulphonethalein excretion was very low. Albumin and numerous hyalin and granular casts were found in the urine. With this there was an increasing hypotension, the systolic blood pressure averaging about 90.

The calcium and phosphorus metabolism was studied. On a calcium intake of about 0.5 gm. daily there was a definitely negative balance, with more calcium in the stools than was taken by mouth, and with an abnormal excretion of calcium in the urine considering the presence of a marked renal insufficiency.

A remarkable change in her general condition occurred during a period of eight days on a high calcium intake. The serum calcium rose to 17.8 mg. per 100 cc. and she became drowsy and irrational. During the latter part of this period she developed signs which were interpreted as cardiac failure; a marked tachycardia, dyspnea, râles at the lung bases and dependent edema. It seemed possible that this striking change was due to the influence of the high serum calcium on the nervous system and on the heart. Prompt lowering of the serum calcium seemed imperative. This was accomplished by the administration of neutral sodium orthophosphate by mouth and attended with obvious improvement. A few days later, however, she developed a bronchopneumonia from which she died on December 24, 1929.

At autopsy the muscles were found to be greatly atrophied. The whole body was extremely emaciated. There were fibrous-tissue adhesions about the operative scar on the abdomen, around the cecum and extending to the liver. In the lungs there were small areas of bronchopneumonia. The pleuræ were bound together in places by slight adhesions. Small stones were seen in the gall bladder and in the cystic duct. The thyroid was not enlarged but contained a few adenomata and a small cyst. On the posterior surface of the thyroid there were several large smooth bodies lighter in color than the thyroid tissue. Of six of these which were removed, three were found to be parathyroid glands.

The largest measured 11 by 5 mm. The vertebral bodies, ribs and clavicles were softened and cut easily with a chisel.

The chief interest of the autopsy attached to the microscopic findings. The parathyroid glands showed an essentially normal arrangement and structure. It was remarked, however, that the cytoplasm of the cells appeared swollen and vacuolated as though they were in active secretion. In one area of the gland there were larger cells with clear cytoplasm and nuclei.

The predominating type of cell in the bone marrow was large with a clear eccentric nucleus. The nucleolus was well defined and fine strands of stromata were condensed at the periphery, giving a typical cogwheel character to the nucleus. The cytoplasm was egg-shaped in most cases and the eccentric nucleus was placed near to one end. The appearance of these cells was considered typical of plasma cells. The changes were present in vertebræ, clavicles and ribs.

Metastatic calcification was found in the lungs, gastric mucosa and kidneys. In addition to areas of bronchopneumonia, there were in the lungs networks of blue staining material. Close examination revealed that this was calcium in the walls of the alveoli. In some places it extended in long straight lines as though following along bloodvessels, while in others it was accumulated in thick, dark irregular patches suggesting deposits with relation to bloodvessels. Sometimes it formed a ring around small capillaries which were filled with red blood cells. In the gastric mucosa there was a deposit of calcium which surrounded the base of gastric glands, forming a partial network about them. In other areas it clearly outlined the bloodvessels. In still other places it seemed to replace the cells of the gastric mucosa itself. These changes were limited to the distal portion of the gastric mucosa. Iron stains indicated the presence of iron in those areas where calcium was found.

The kidneys were involved in chronic degenerative change. The cortex was thin, with many scarred areas infiltrated with lymphocytes. Many glomeruli were completely fibrosed and hyalinized. Tubules were scarred and dilated and many of them were filled with hyalin casts. In some areas, especially in the pyramidal portion of the organ, deposits of calcium similar to those in the lungs and stomach were seen. Some formed a fine shell about the collecting tubules, while others extended into or replaced kidney cells. Some deposits outlined bloodvessels. In the cortex of the kidney such deposits were rare. As in the other organs, iron was found wherever abnormal calcium deposits had formed.

In this case, as in the others, there was hypercalcemia and an abnormal excretion of calcium in the urine. The metastatic calcification was in distribution and character in no way distinguishable from that which has been seen in von Recklinghausen's disease. The measurements of the parathyroid glands greatly exceeded the normal limits given by Cowdry.¹¹ If the normal range of Biedl¹³ be accepted there might be some question concerning hyperplasia. Considering both clinical and pathologic data, however, there seems to be no doubt that hyperfunction of the parathyroids existed in this patient. The pathologic appearance of the bone marrow was characteristic of multiple myeloma of the plasma-cell type.

High values of serum calcium have been found in other cases of multiple myeloma. In Charlton's⁹⁹ patient it varied from 12 to 16 mg. Durman's¹⁰⁰ case had 16.1 mg. and Belden's¹⁰¹ case, in which the diagnosis was not completely established, values ranged from 15.3 to 18.7 mg. Francis Smith¹⁰² has recently studied 2 patients with multiple myeloma, both of whom had high serum calcium. In a patient whom we observed at the St. Louis City Hospital the serum calcium was 13.4 mg.

Metastatic calcification, while by no means constant in this condition, has been frequently observed. Permin,¹⁰³ Froboese¹⁰⁴ and others have shown calcium deposits in the kidneys. Austin¹⁰⁵ found them in the

lungs; Froboese in the uterine mucosa and Tschistowitsch and Kolessnikoff¹⁰⁶ in the ventricles.

The kidneys are seldom normal in multiple myeloma, although no constant renal picture has been associated with the disease. In this case it is possible that there was kidney insufficiency at the time the patient was first studied and that it may have influenced the calcium and phosphate content of the blood. In terminal nephritis, however, there is generally a tendency to hypocalcemia and to great increase in phosphate, conditions exactly opposite to those found in our patient.

The question of the relationship of nephritis to metastatic calcification is interesting. It is well known that abnormal deposits of calcium are found in the nephritis of mercury poisoning. In several patients exhibiting metastatic calcification in von Recklinghausen's disease there has been a coëxisting damage of the kidneys. This was true in the cases of Hoffheinz²⁸ and of Dawson and Struthers,³⁹ and particularly notable in the case of Hubbard and Wentworth.³³ It seems possible that metastatic calcification in *ostitis fibrosa* and in multiple myeloma may depend both on hypercalcemia and insufficient kidneys.

Bergstrand,³⁴ MacCallum⁵⁹ and others have found parathyroid hyperplasia in patients with chronic nephritis but with no bone disease. The possibility that some part or all of the parathyroid changes in this case are due to nephritis cannot be excluded.

CASE IV.—A young woman, aged twenty-four years, entered Barnes Hospital because of a deformity resulting from an old pathologic fracture of the left femur. Her family history and past history were unimportant. She had always been quite healthy. When eleven years of age she fell while running and bruised her left knee. This resulted in little discomfort and symptoms had disappeared within a week. About three months later she began to have a constant dull pain in the left hip which was exaggerated by walking and did not entirely disappear when she was lying down. The pain continued while she was treated in various ways for flat feet. At the age of fourteen years she slipped, fell to the ground and suffered extreme pain in the left hip. Roentgen ray disclosed multiple cystic disease of the upper half of the femur with a pathologic fracture through the neck. At seventeen and again at eighteen years of age the pathologic areas in the femur were curetted and cauterized. She entered Barnes Hospital in October, 1928. Her general health had been good. There were no urinary symptoms; clinical and electrical tests of her muscles disclosed no hypotonicity. She had, at times, slight edema of the left ankle and foot, but none of the right. The general physical examination revealed no abnormalities. There was no anemia. The urine was negative and the Wassermann reactions were negative. Repeated careful examinations for a possible parathyroid tumor were negative. Roentgen ray showed cystic disease of the upper half of the left femur with the head in the acetabulum and the trochanter resting high against the ilium. Although Roentgen ray of the entire skeletal system disclosed no rarefaction, a spindle-shaped enlargement of the middle left metatarsal was found. During her stay in the hospital the head of the femur was resected and the trochanter was drawn down to the acetabulum. Tissue was taken for microscopic study, but was unsatisfactory. The diagnosis of *ostitis fibrosa cystica* was made.

For a period of four months complete studies of the calcium and phosphorus metabolism were made. The serum calcium ranged from 10.3 to 11.3 mg. per cent except in the two weeks following operation, when it fell as low as 8.5 mg. The serum phosphorus varied from 2.6 to 3.9 mg. Before operation the urinary calcium excretion was very low except on an exceedingly high calcium intake, when it mounted to about 500 mg. daily. There was a constant tendency to excrete excessive amounts in the stools. During a period of two months after her operation the calcium and phosphorus metabolism were quite normal.

CASE V.—A girl, aged eleven years, entered the St. Louis Children's Hospital because of a limp which had been present intermittently for seven years. She had always been quite well and strong and was very active. She was a healthy looking, well-nourished girl, showing no abnormality on physical examination except a slight outward bowing of the right thigh. There had never been any pain or tenderness of the right hip. Roentgen ray showed the upper half of the right femur to be greatly enlarged and to contain irregular cystic appearing areas. The midportion of the right tibia presented a similar area. A diagnosis of *ostitis fibrosa* was made. The urine was negative. There was a moderate leukopenia but no anemia. The serum calcium was 10.9; the serum phosphorus was 4 mg. per 100 cc.

In Cases IV and V the onset of the disease occurred in childhood. The Roentgen ray appearance of the bone was typical of *ostitis fibrosa cystica*, and since the symptoms were referred in each case to the femur only, it was thought at first that the patients were suffering from the localized form of the disease. The discovery of lesions in other bones in the metatarsal of Case IV and in the tibia of Case V indicated a condition which could not be sharply differentiated from generalized *ostitis fibrosa*. There was, however, no evidence of hyperparathyroidism. No tumor could be found in the thyroid region. The muscles exhibited no hypotonia; kidney stones were not apparent; the values for serum calcium were within normal limits and in Case IV extensive studies of the calcium excretion revealed no definite abnormalities.

Discussion. CLINICAL RECOGNITION OF HYPERPARATHYROIDISM. Several of the manifestations of experimental hyperparathyroidism are of a character which could be recognized if they occurred in the examination of a patient. Most of them, however, are not sufficiently distinguishing to be of crucial diagnostic importance. Kidney stones appear in many other conditions. Muscular weakness, diminished muscle tone or even a lowered excitability of muscles cannot be considered significant of any single malady. Increased urinary excretion of calcium might be a valuable diagnostic sign, but its study is always laborious and can be attempted only with special facilities. The level of blood calcium, on the other hand, is simply determined, and, although extensive studies have been made, hypercalcemia has been discovered in only a few conditions. In the consideration of our patients its presence was interpreted as evidence of an increased activity of the parathyroid glands. In the case of multiple myeloma it was the only clinical sign which suggested the possibility of parathyroid disease. It is important to inquire whether hypercalcemia may be considered as a pathognomonic sign of hyperparathyroidism.

Although it has been stated that calcium in the diet exerts an influence upon the level of serum calcium, the contention has not been established. Roe and Kahn¹⁰⁷ found that the ingestion of 5 gm. of calcium lactate by mouth caused hypercalcemia sometimes as high as 16 to 19 mg., the maximum change occurring from four to six hours after the ingestion. Bauer and Ropes¹⁰⁸ were unable to confirm this. Even with 10 gm. of calcium lactate they were never able to increase the calcium content of serum above 12.5 mg. Limited observations in our own clinic have shown no calcium figures higher than 13 mg. following the ingestion of calcium.

Hess¹⁰⁹ and others have demonstrated that experimentally the calcium content of serum may be artificially increased by the use of radiated

ergosterol. It has not been shown, however, that a comparable condition can occur spontaneously or can be recognized as a clinical entity.

Coates and Raiment¹¹⁰ report values averaging 19 mg. per 100 cc. of serum in cases of gout. This has not been confirmed by Hench¹¹¹ and is questioned by Cameron.¹¹² Most interesting are the reports of hypercalcemia in arthritis deformans. Horwitz found values as high as 16.2 mg. in 5 of 14 cases. Mark¹¹³ observed 4 cases in which values ranged from 13.3 to 20.3 mg. Nachlas,¹¹⁴ however, was unable to find hypercalcemia in any one of 19 cases of osteoarthritis or in 18 cases of rheumatoid arthritis. Hench also failed to find this condition in 25 cases of infectious arthritis studied at the Mayo Clinic. Koenig and Bulger,¹¹⁵ in our own clinic, were unable to find a single example of hypercalcemia in 82 determinations on 30 arthritic patients.

Recently Brown and Roth¹¹⁶ have reported values for calcium ranging from 11.1 to 18.1 mg. in patients suffering from polycythemia vera. When phenylhydrazin was given and the number of red blood cells diminished the serum calcium was found to be lower.

While evidence concerning the occurrence of hypercalcemia in some of these conditions is conflicting, it is apparent that several diseases must be considered when high values of serum calcium are encountered. Joint diseases, polycythemia, abnormal ingestion of calcium or of irradiated ergosterol may, however, be recognized from examination and history and should cause little confusion in diagnosis.

The mechanism of the supposed hypercalcemia of gout and of arthritis and of the changes in polycythemia is not established. The work of Hess¹⁰⁹ indicates that radiated ergosterol does not cause high calcium values if the parathyroids have been removed. Except in the state following ingestion of large amounts of calcium, hyperparathyroidism may be considered as a possible cause of hypercalcemia in all of the conditions which have just been mentioned as well as in *ostitis fibrosa*, carcinomatous metastases in bone, multiple myeloma and nephritis—diseases in which parathyroid tumors or hyperplasia have been demonstrated.

The belief that the hypercalcemia of *ostitis fibrosa cystica* is due to hyperparathyroidism rests upon the fact that several of the accompanying symptoms: increased urinary excretion of calcium, abnormal deposit of calcium in tissues and muscle weakness are found in experimental overdosage with parathormone; upon the finding of parathyroid hyperplasia and tumors and upon the fall in serum calcium which accompanies the removal of a parathyroid tumor.

In multiple myeloma and in carcinomatous metastasis to bones the evidence is not so convincing. The parathyroid hyperplasia in our case of myeloma and the parathyroid tumor in Klemperer's³⁷ case of metastatic cancer indicate that the hypercalcemia observed clinically may have reflected increased function of the parathyroid glands.

From the evidence which has been presented, it appears that hypercalcemia should always arouse suspicion of hyperparathyroidism. It is, moreover, the only clinical sign which is of crucial diagnostic importance in the recognition of hyperparathyroidism, since a study of urinary calcium excretion is seldom feasible. Nephrolithiasis and hypotonia of

muscles must be considered important when they occur with hypercalcemia, but cannot be considered diagnostic when found alone.

It is possible that hyperparathyroidism may exist in the absence of hypercalcemia. The parathyroids are only one factor in the maintenance of the serum calcium level. The absence of vitamin D or of sunlight may be mentioned as causative in the low calcium values found in rickets. The recent work of Nitschke¹¹⁷ indicates that the thymus and lymph nodes may be effective in lowering serum calcium. In nephritis the retention of phosphate is accompanied by hypocalcemia. In rickets both of animals and of children and in some cases of nephritis hyperplasia of the parathyroids has been demonstrated. This may represent a need for increased parathyroid function and may be secondary to factors having a tendency to reduce the level of serum calcium. Thus one could consider the serum calcium value in a case of rickets a resultant of two opposing factors, the absence of vitamin D tending to lower it while the enlarged parathyroids tend to raise it. Hyperparathyroidism, in the sense of increased functional activity might exist without hypercalcemia or, indeed, in the presence of low values of serum calcium.

RELATION OF HYPERPARATHYROIDISM TO VON RECKLINGHAUSEN'S DISEASE AND OTHER DISEASES OF BONE. The question of the relationship of parathyroid changes to bone disease presents many difficulties. Erdheim, after studying the parathyroids in rickets, postulated that the hyperplasia of these glands is secondary to changes in the bone and acts as a compensatory or conservative process. This reasoning was applied to other conditions in which parathyroid and osseous changes were found to be associated. Mandl⁴⁸ attempted to test the theory. He removed the parathyroid glands from a man dying as a result of an accident and engrafted them in his patient with *ostitis fibrosa cystica*. If Erdheim's theory applied to this condition improvement should have resulted. Actually the patient became worse. Mandl then removed the parathyroid tumor, an operation which, as has been related, caused striking improvement in the symptoms of the disease. Quite naturally he concluded that his experiment disproved the application of Erdheim's theory to von Recklinghausen's disease.

One is tempted to go farther than Mandl and to state that *ostitis fibrosa* is secondary to hyperparathyroidism. Many of the symptoms which are identical with those of experimental parathyroid administration disappear after removal of parathyroid tissue. While cysts and giant-cell tumors of bone have not been demonstrated in experimental hyperparathyroidism, it might be assumed that these changes are incidental and follow injury in bones already softened by disease. The explanation receives some support from the frequent occurrence of hemorrhage in the cysts and from the pathologic studies of Looser, who suggests that the cysts and giant-cell tumors are the results of greenstick fractures in softened bone. One set of clinical observations seems to support the contention that the tumors are associated with parathyroid changes. Removal of the parathyroid tumor in Case I caused a regression in the size of the two cysts. No new tumors appeared, which is remarkable when it is remembered that at least two tumors had appeared during the year preceding her operation. In Case II no new swellings were detected after the parathyroid tumor was removed.

In the literature we have found no record of the appearance of cysts or tumors of the bones following parathyroidectomy.

Although the idea that the parathyroids may be entirely responsible for the changes of *ostitis fibrosa* is sufficiently alluring, it must not be accepted without reservation. It is significant that solitary cysts and single giant-cell tumors which are pathologically so similar to the multiple bone tumors of von Recklinghausen's disease, may exist without evidence of changes in the parathyroids. Moreover, in 2 of our cases (Case IV and V) there was multiple fibrocystic disease without hypercalcemia. In Case IV, which was thoroughly studied, there was no demonstrable disturbance in calcium metabolism. These cases demonstrate at least that similar pathologic changes may arise in bones from causes other than obvious hyperparathyroidism.

At the time our first patient came under observation the symptoms referable to increased parathyroid function were predominant. This was true also in the patients of Mandl, Gold, Du Bois and Wilder, and particularly in Snapper's case, in which all evidences of *ostitis fibrosa* had disappeared in an extraordinary degree of decalcification of the bones. But even in these cases, where parathyroid symptoms are most notable, it cannot be asserted that hyperparathyroidism is the primary factor in the disease. It is possible that bone changes occur first and stimulate the parathyroids to an increased activity which, in turn, aggravates the condition in the bones. If such an explanation is accepted, Cases IV and V of our series might be regarded as early stages of *ostitis fibrosa cystica* in which the secondary parathyroid changes had not yet become notable.

There seem to be no entirely valid reasons for deciding whether parathyroid hyperplasia is primary or secondary in *ostitis fibrosa*. In multiple myeloma, on the other hand, the probability is great that it is secondary to the bone changes. It cannot readily be assumed that a neoplastic process widely distributed through the body results from parathyroid hyperplasia. Neither can one believe that parathyroid changes were primary in Klemperer's case of carcinoma of the breast which metastasized to bone. The conditions seem comparable to those observed by Erdheim in rickets and by Thomas in osteomalacia. It is probable that many generalized diseases of bone, accompanied by extensive absorption or destruction of bone substance, lead eventually to significant parathyroid hyperplasia. In multiple myeloma, however, as in *ostitis fibrosa*, it may be possible for the hyperparathyroidism to become so active that it constitutes a menace in itself and assumes a predominant rôle in the clinical picture.

Summary. 1. The symptoms of clinical hyperparathyroidism are similar to those produced by the experimental injection of excessive amounts of parathormone. They include hypotonia and diminished electrical excitability of muscles, decalcification of bones, hypercalcemia and abnormal excretion of calcium in the urine. In some cases there is nephrolithiasis. Hypophosphatemia has been observed.

2. Hypercalcemia is the most significant clinical sign in the diagnosis of hyperparathyroidism. Although it may be found in a few other conditions, its presence usually indicates increased function of the parathyroid glands.

3. Hyperplasia of the parathyroids and clinical evidence of hyper-

parathyroidism have been found in many cases of generalized bone disease, including rickets, puerperal osteomalacia, multiple myeloma and carcinomatous metastases to bones. The parathyroid changes appear to be secondary to the changes in bone. While in some cases the increased function of the parathyroids may possibly serve a useful function, in other cases it becomes actually harmful by increasing the decalcification of the bones.

4. In generalized *ostitis fibrosa cystica* (von Recklinghausen's disease) the clinical picture of hyperparathyroidism is most frequently encountered. It may possibly be primary and is unquestionably harmful. In such cases removal of parathyroid tissue has accomplished clinical improvement and apparent arrest of the progress of the bone disease.

5. Determinations of the calcium and phosphate content of the serum should be made in all cases of generalized bone disease not only as a matter of interest but because of their therapeutic indications.

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HYPERTHYROIDISM AND PREGNANCY.*

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HYPERTHYROIDISM and pregnancy in the same patient is a combination of great interest and importance to both surgeons and obstetricians. For many years it has been known that simple thyroid enlargement appears in many pregnancies. In goiter belts as high as 40 to 60 per cent of the pregnant women are known to have simple goiters,^{9,16} and in nongoiter areas some thyroid enlargement during pregnancy is frequently noted. In this study, however, we do not wish to consider the incidence or importance of this type of simple goiter during pregnancy. We shall concern ourselves entirely with the study of hyperthyroidism as it complicates pregnancy, and of pregnancy as it is complicated by hyperthyroidism.

The objects of this study were to determine: (1) What the effect of hyperthyroidism is on pregnancy: Does pregnancy end disastrously when hyperthyroidism is present any more commonly than in normal women? (2) What effect has pregnancy on the course of hyperthyroidism? Does pregnancy increase or diminish the thyroid intoxication? (3) What effect has hyperthyroidism during pregnancy on the baby? Is congenital goiter or any other abnormality more common in babies born of thyrotoxic mothers? (4) What effect does pregnancy play in the causation of hyperthyroidism and what effect has pregnancy coming after thyroidec-tomy for hyperthyroidism in the recurrence of the hyperthyroidism?

For the first part of this study we have gone over the clinical records of all the thyroid patients treated in the Lahey Clinic from 1914 to August 1, 1929, and have selected all patients having both hyperthyroidism and pregnancy. Thirteen cases of exophthalmic goiter and pregnancy and 2 cases of secondary hyperthyroidism and pregnancy were found. In this interval there were 3678 toxic patients operated upon. Of this group 887 were adenomatous goiter with secondary hyperthyroidism and 2791 patients had primary hyperthyroidism. The incidence of pregnancy then in hyperthyroidism, in our experience, is 0.41 per cent. It is common knowledge that the incidence of hyperthyroidism in pregnancy is very low. Thus, there were no cases of hyperthyroidism in 937 obstetrical cases discussed by Yoakum.⁹ At the Mayo Clinic¹⁸ only 42 cases of pregnancy were found in 7228 cases of hyperthyroid-

* Read before the Boston Obstetrical Society, October 15, 1929.

ism (0.6 per cent). These figures clearly show the relative infrequency of hyperthyroidism in pregnancy. The fact that diminution of the menstrual function often accompanies thyroid toxicity and that the more severe the hyperthyroidism the less active is ovarian function, may well be related in some degree to the lack of fertility in thyrotoxic women.

In any discussion of hyperthyroidism during pregnancy a word of caution must be given as to the diagnosis of hyperthyroidism in pregnancy. It is known that during the later months of pregnancy the basal metabolism in a normal woman tends to rise to a relatively small degree (+25 to +30 per cent) above normal. This increased rate is not to be interpreted as evidence of hyperthyroidism but as due to the presence of an increased protoplasmic mass.^{16,18,19,21} Before the diagnosis of hyperthyroidism can be made in any case, therefore, it is essential that in addition to a slight elevation in basal rate many positive symptoms and signs of the disease be present. We believe the metabolism must be elevated well above normal and probably above +30 per cent and a hyperplastic thyroid gland with tachycardia and definite activation should be present before a final diagnosis of hyperthyroidism in pregnancy can be safely established. It is very common to find tremor, nervousness and rapid heart in women, and when, in addition to these symptoms the enlarged thyroid gland of pregnancy is discovered, a diagnosis of hyperthyroidism may be too readily made.

What effect has hyperthyroidism on the course of pregnancy? Opinions on this point are not at all uniform, thus Gardiner-Hill¹ finds in a study of numerous statistics published in the literature that the results of pregnancy in exophthalmic goiter were very poor and 50 per cent of the cases ended in miscarriage or premature births. On the other hand, experience at the Mayo Clinic tends to show very definitely that no more abortions, miscarriages or premature births occur when the complication of hyperthyroidism is present than in normal women. Our experience coincides with this. We have found in our records 18 patients who had definite hyperthyroidism while pregnant. Sixteen of these women had primary hyperthyroidism (exophthalmic goiter) and 2 had adenomatous goiter with hyperthyroidism. Three of the 18 patients had thyroidectomies after their delivery, but were not operated upon while pregnant. Subtotal thyroidectomy was carried out in the remaining 15 cases of these women during their pregnancy and all the mothers recovered. One woman miscarried two days after a long ride home by automobile from the hospital. The miscarriage was eight days after her operation and her physician informs us that he saw no other cause for it than possibly the long ride. The 3 women not operated upon until after delivery had normal deliveries and later did well after thyroidectomy. We may conclude,

therefore, that hyperthyroidism does not cause a disastrous termination of the pregnancy in the majority of cases.

The second problem in this study, namely, what is the effect of pregnancy on hyperthyroidism, is not so readily answered. There are so many factors influencing every case of hyperthyroidism that it is always difficult to establish one as more significant than another in analyzing the end result. Furthermore, unless one has basal metabolism studies with due allowance for the normal elevation in rate of late pregnancy, it is difficult to know what criterion can be accepted as to the effect of the pregnancy on the hyperthyroidism. H. Gardiner-Hill¹ and Hyman and Kessel⁷ believe that there is no evidence that pregnancy makes thyrotoxic cases worse, but, on the contrary, that many cases improve during pregnancy and maintain their improvement afterward. L. Seitz⁴ believed that pregnancy did not affect the hyperthyroidism in 40 per cent of his cases, but that in 60 per cent the hyperthyroidism was made much worse by the pregnancy. Mussey, Plummer and Boothby¹⁸ do not find that pregnancy makes the course of hyperthyroidism any more difficult to handle or influence it to any degree. We have not seen anything occur in any woman with hyperthyroidism and pregnancy which does not commonly occur in nonpregnant thyroid cases of that type. Multiple-stage thyroidectomies have been just as necessary in pregnant as in nonpregnant women, but no more so (20 per cent had multiple-stage operations). We believe, however, that pregnancy during hyperthyroidism is certainly a very definite added load for the patient to endure whether or not it affects the degree of hyperthyroidism which is present. Pregnancy must increase the patient's muscular work and add to the metabolic requirements. It is our daily experience that thyrotoxic patients cannot tolerate additional loads, and we feel certain that from this point of view, at least, pregnancy is a serious burden in all severe thyroid intoxications.

The third problem that we hoped to answer in this study was what effect hyperthyroidism during pregnancy would have on the baby. In all our cases of hyperthyroidism which went to term and had living babies, all the babies were normal. There were in this group no congenital defects, no goiters and no evidence of insufficient thyroid function, that we were able to trace through either the mothers or their physicians. We have not discovered in these cases any evidence which even suggests that a baby born of a thyrotoxic mother will be abnormal in any way.

The possibility that pregnancy is related to the occurrence of hyperthyroidism has frequently been suggested. The fact that pregnancy is so commonly accompanied by some thyroid enlargement has doubtless given strength to this suggestion. Any proof of this theory, however, is necessarily difficult, and statistical studies, unless very striking, may well be misleading. We have, therefore,

gone over the histories of 602 consecutive patients with hyperthyroidism and attempted to learn something of the relationship between the occurrence of pregnancy and the onset of hyperthyroidism.

It was necessary to exclude certain of these 602 cases from this study. Thus 85 were males; 14 were under eighteen years of age; 155 were married and over the childbearing age; 49 were single and over thirty-five years of age; 7 records were unsatisfactory. There were, therefore, 292 cases to whom letters could be sent and who could be investigated. Of these, 203 replied to our inquiries. These 203 replies from women of childbearing age form, therefore, the basis of this section of our study of the relation between pregnancy and the onset of hyperthyroidism.

In this group there were 41 women who stated that the onset of their hyperthyroidism was dated within three months of delivery. That is to say, of the 510 women of the large group, 41, or 8 per cent, said their pregnancy and their hyperthyroidism occurred within three months of each other and might be related. If we consider only the 347 women in the group who were married, however, it would be true that roughly 12 per cent of the married women had been pregnant within three months of the onset of their hyperthyroidism. This is not, in our opinion, such an outstanding or remarkably striking relationship that it will permit any deductions that pregnancy was or was not a factor in the onset of the hyperthyroidism.

Our figures tend to prove that there were, if anything, fewer pregnancies before the onset of hyperthyroidism in this group than are to be expected in any ordinary group of women: 118 of the 203 women who answered our inquiries were married and under forty years of age; 90 of these women had had at least one pregnancy before the onset of their hyperthyroidism. If it be admitted that 10 per cent of all marriages are childless it is seen that 90 pregnancies in 118 women is definitely below the normal expectation. We believe that these findings tend to prove that pregnancy cannot be considered an etiologic factor in hyperthyroidism.

Our belief that pregnancy is not a factor in exciting hyperthyroidism is further borne out by our study of pregnancy occurring after thyroidectomy for exophthalmic goiter. Fifty-three of the 203 women bore 69 children after thyroidectomy and only in 1 case was there even a question of any recurrence of thyrotoxic symptoms during the pregnancy and puerperium. In this 1 case the physician reported that he suspected some return of thyroid toxicity but had been able to control it completely with Lugol's solution. Such a case may or may not be a recurrence of hyperthyroidism during pregnancy. At any rate, the fact that 69 pregnancies failed to produce any serious return of hyperthyroidism in any one of 53 postoperative hyperthyroidism patients is, in our opinion, very

excellent evidence that pregnancy is not a potent factor in the etiology of hyperthyroidism.

The results of the 69 pregnancies are also known: 47 of the babies had been born normally and were healthy children; 8 babies were unborn at the time of our study and 14 of the babies failed to live from either miscarriage, abortion or disease of the newborn. In 13 of these cases there was no relationship between the previous thyroid disease or operation and the fetal death. In 1 case the cause of fetal death was unknown. The loss of 14 babies in 69 pregnancies is a mortality of 20 per cent. This figure is certainly within the normal expectation of abortion or miscarriage in pregnancy among a group of normal women. In fact, many obstetricians recognize a much higher figure as much more probable among all types of women. We, therefore, feel that subtotal thyroidectomy for hyperthyroidism does not render future pregnancy unusually dangerous to the baby.

Seven of the women in this particular group of cases were pregnant at the time that thyroidectomy was performed. All the mothers recovered and all the pregnancies terminated normally save in 1 case, which ended in a miscarriage about two weeks after the thyroidectomy. No cause for this miscarriage could be determined and we cannot say that it was or was not related to the thyroidectomy. This group of 7 cases gives us reason to believe that thyroidectomy for exophthalmic goiter can be undertaken during pregnancy with safety to both mother and child if the usual safeguards of thyroid surgery are carefully maintained.

Conclusions. 1. In this Clinic the incidence of pregnancy in 3678 cases of hyperthyroidism was 0.41 per cent.

2. Special care is needed that the normal elevation of metabolism in late pregnancy is not interpreted as evidence of thyroid disease.

3. Hyperthyroidism does not cause an unnatural termination of the pregnancy in the majority of cases when it is properly treated.

4. We believe that pregnancy does not increase the toxicity of primary hyperthyroidism except as the increased proplasmic mass of pregnancy brings some increase in metabolism. Pregnancy is, however, distinctly an added burden in hyperthyroidism, which should be avoided if possible.

5. Babies born of thyrotoxic mothers are not abnormal.

6. Pregnancy does not appear to be a cause of primary hyperthyroidism.

7. Pregnancy after thyroidectomy for primary hyperthyroidism does not cause recurrence of thyroid toxicity.

8. Babies born of mothers who have had thyroidectomy for hyperthyroidism are normal.

9. Thyroidectomy for primary hyperthyroidism can be undertaken during pregnancy with safety to both mother and child.

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THE EFFECT OF INSULIN ON PATHOLOGIC GLYCOGEN DEPOSITS IN DIABETES MELLITUS.

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Introduction. Since Ehrlich,¹ in 1883, found in 14 cases of diabetes the peculiar glycogenic infiltration of the epithelium of Henle's loops in the kidneys, this lesion has been regarded as the most definite anatomic finding in active diabetes mellitus. Other less constant abnormal glycogenic deposits associated with the disease were also noted by Ehrlich: the increased glycogen in the heart muscle fibers; glycogenic granules in the leukocytes; and large glycogen-filled vacuoles in the liver cells. Curiously enough, it was not until twenty-three years later that Meixner,² soon followed by Best,³ demonstrated the glycogen-filled vacuoles in the epithelial cells of the liver to be the nuclei.

It is hardly fair to say that glycogenic infiltration of the epithelium of Henle's loops is definite evidence of diabetes mellitus, as glycosuria, from any cause, gives rise to this change. Thus Gierke⁴ states it has been found: (1) in diabetes mellitus; (2) after experimental extirpation of the pancreas; (3) after extirpation of the celiac plexus; (4) in phloridzin poisoning.

In the first 3 instances the blood-sugar level is increased, in the last it is normal, or low. The one point in common is the presence of glucose in the urine.

Since, in the great majority of cases, glycosuria in the human means diabetes, the presence of glycogen in Henle's loops may be interpreted as an indication of active diabetes.

It is rather interesting that Ohohashi⁵ finds that the distribution of glycogen in the diabetic kidney is exactly the same as that in the normal kidney of the anura. In normal frogs he found traces of glycogen even in the leukocytes. He also mentions that glycogen occurs in the epithelium of the pancreatic ducts in mammalian fetuses. I have found it in this location in several cases of diabetes.

Loeschke⁶ gives the following table based on 6 cases of diabetes, showing the glycogen present elsewhere in the kidneys besides Henle's loops:

TABLE I.—AMOUNT OF GLYCOGEN IN RENAL EPITHELIUM (LOESCHKE).

Case.	Glomeruli.	Convolved tubules.	Henle's loops.
I	+++	+++	++
II	++	+	+++
III	+	+	++
IV	—	+	++++
V	—	—	+
VI	—	—	+

Rosenberg⁷ also mentions a case in which glycogen was present in the glomeruli and epithelium of the convoluted tubules, as well as in Henle's loops. In certain of the cases summarized in this paper, I have found a similar distribution of the glycogen. Sandmeyer⁸ gives a quantitative determination of the glycogen present in the kidney of a girl, aged nine years, who had had diabetes for two years, 0.1158 gm. per 100 gm. of kidney substances. The liver contained 0.6130 gm. per 100 gm., or nearly six times as much.

Since pathologists have considered for years that one of the most constant signs of diabetes is the occurrence of glycogen in the epithelium of Henle's loops, it was somewhat disconcerting to me to find in undoubted cases of diabetes mellitus no evidence of abnormal glycogen deposits. In some of these cases glycogen was present in the liver cell nuclei, but it has long been known that there are many conditions other than diabetes in which there is this intranuclear deposit of glycogen. In fact, approximately one-third of all post-mortem examinations show this deposit to a greater or less degree.^{9,10}

Methods. While Best's carmine stain probably is not entirely specific for glycogen, it is none the less the most satisfactory method available for demonstrating this substance. Tissue from surgical specimens or from autopsies is fixed in absolute alcohol and celloidin sections are cut and stained by the Best technique given by Mallory and Wright.¹¹ As controls, sections placed in saliva for ten minutes

were also stained. In certain cases the iodine method of Langhans was also used.

In renal epithelium and liver-cell nuclei the presence of vacuolization as shown in paraffin sections with various stains is a further aid. This vacuolization runs closely parallel with the glycogen content as shown by Best's stain in tissues fixed under one hour post-mortem, and is much more marked than the carmine stain would indicate in tissues fixed a longer time postmortem.

In most tissues there is a rapid drop in demonstrable glycogen in the first hour after death, and but little change for some hours thereafter. Yater, Osterberg, and Hefke¹² found by microchemical analysis that one-half to three-fourths the glycogen in the rabbit disappears in the first hour, and that from then on the rate of decrease is slow.

Results. Both surgical and postmortem material has been utilized, and the glycogen distribution studied in the various tissues, particularly heart, liver, kidneys, pancreas, voluntary muscle and skin. Both insulin treated cases of diabetes and cases not treated with insulin are included, as well as a control series of non-diabetics.

Heart. Glycogenic infiltration of the heart muscle is marked in many cases of diabetes. It is particularly striking in those fibers at the margins of infarcts. It can also be found there longer post-mortem. Whether this means greater storage of glycogen or that the fibers are damaged and so deficient in glycogenolytic ferment is somewhat difficult to decide. On the basis of tissue fixed under thirty minutes postmortem an abnormally large storage of glycogen seems the more likely.

So far as the amount of glycogen in the muscle as a whole is concerned, there is but little difference between the insulin treated cases of diabetes and the control series. The diabetic cases not treated with insulin show a high proportion of heavy deposits of glycogen.

TABLE II.—GLYCOGEN CONTENT OF HEART.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	5	3	5
Insulin	1	..	1
Insulin, infection present	..	3	7	4
Control (nondiabetics)	2	4	11	3

Liver. Since glycogenic distention of the nuclei of liver cells is found in many other conditions than diabetes, this cannot be regarded as of particular importance. However, in diabetic patients there is a very definite reciprocal relationship between the amount of intranuclear and the amount of intracytoplasmic glycogen. When intranuclear glycogen deposition is marked, there is but

little or even no glycogen in the liver cells in these cases. Conversely, when there is much glycogen stored in the cytoplasm, there are few or no nuclei containing it.

TABLE III.—LIVER CELL NUCLEI.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	1	8	5	7
Insulin	7	5	1	..
Insulin, infection present	3	8	7	4
Control (nondiabetics)	10	6	3	1

Glycogen is most marked in those cells in the periportal region. Frequently the cells about the central vein contain none, although it is present elsewhere in the lobule in large amounts. There is no antagonism between the deposition of fat and glycogen, both being often present in the same cells in large amounts.

TABLE IV.—GLYCOGEN CONTENT OF LIVER CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	4	4	5	1
Insulin	1	2
Insulin, infection present	2	6	3	5
Control (nondiabetics) .	..	9	9	4

The above table gives indisputable evidence of the effect of insulin in promoting the deposit of glycogen in the liver, although this effect is somewhat lessened in septic cases.

Pancreas. In 8 instances considerable amounts of glycogen and in 10 instances slight amounts were found in the epithelium of the pancreatic ducts, both the smaller ducts with cuboidal epithelium and the larger ducts with columnar. As has already been mentioned Ohohashi⁵ found this distribution in mammalian fetuses. I have encountered glycogen nowhere else in the pancreas.

TABLE V.—GLYCOGEN CONTENT OF PANCREATIC DUCT CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	4	5	3	2
Insulin	4
Insulin, infection present	11	5	3	..
Control (nondiabetics)	22

Kidneys. Insulin treatment definitely reduces the amount of glycogen present in the kidneys. In many cases it is entirely absent. In many others it is considerably reduced over that found in cases of diabetes not treated with insulin. Although Henle's loops are the most typical loci for glycogenic infiltration, the convoluted tubules as well are occasionally involved. Glycogenic

granules may even be demonstrated within the capsular space, but these probably are artefacts due to postmortem diffusion.

TABLE VI.—GLYCOGEN CONTENT OF KIDNEY.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	3	7	3	16
Insulin	6	3	..	1
Insulin, infection present	1	12	6	3
Control (nondiabetics)	15	1

Voluntary Muscle. Many specimens of muscle came from legs amputated for gangrene. They, therefore, may possibly be of dubious value owing to the influence of an impaired circulation, which would certainly interfere with normal cellular function, and might well influence the function of glycogen storage. However, the muscle was always taken from as near the site of amputation as possible. In the autopsy material, portions of the pectoralis major were utilized.

There is an apparent tendency for decrease in muscle glycogen in the cases of diabetes

TABLE VII.—GLYCOGEN CONTENT OF VOLUNTARY MUSCLE.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	1	3	1
Insulin	1	..
Insulin, infection present	1	13	11	6
Control (nondiabetics)	..	7	12	8

Skin. Unna¹³ has recently called attention to the large amount of glycogen in normal skin. Before learning of his work, I had found large amounts of glycogen in the skin of normal individuals, and lesser amounts in the skin of diabetics. The epithelium of the stratum corneum, sweat glands, sebaceous glands and follicles are heavily loaded. Becker¹⁴ speaks of much glycogen in the duct cells of sweat glands in newborn infants. In a few cases the erector pili muscles show heavy deposits. Dr. H. C. Trimble is very kindly making determinations of glycogen and sugar in normal and diabetic skins.

TABLE VIII.—GLYCOGEN CONTENT OF SKIN.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	3	..	1
Insulin	1
Insulin, infection present	3	7	6	4
Control (nondiabetics)	..	3	15	18

Brain. In this series so few permissions for postmortem examination of heads have been received that there are insufficient data available. Geipel¹⁵ found glycogen in the cortical cells of 14 out of 19 cases dying of diabetic coma.

Leukocytes. Glycogenic granules were found in the leukocytes of the granulocytic series in 18 cases of diabetes, all of which showed extensive deposits elsewhere typical of diabetes.

TABLE IX.—GLYCOGEN CONTENT OF LEUKOCYTES.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	1	3	6
Insulin	1
Insulin, infection present	..	4	3	..
Control (nondiabetics) .	2	8

Discussion. Practically every case of active diabetes treated in the preinsulin days showed glycogenic infiltration of the epithelium of Henle's loops at autopsy. The presence of this lesion in cases of glycosuria makes one wonder whether or not it represents an attempt of the tubular epithelium to salvage some of the glucose being lost in the urine. Its absence in many cases treated with insulin shows that it is not an essential lesion of diabetes. This is also indicated by its presence in phloridzin diabetes.

There is close correspondence between increase in liver-cell glycogen and decrease in renal glycogen, and a similar relationship between liver-cell glycogen and liver-nucleus glycogen. As normal storage increases under the influence of insulin, pathologic storage decreases. This holds true in other organs as well. A diabetic responding satisfactorily to insulin treatment, and dying of some condition other than diabetes or sepsis, such as cerebral hemorrhage, shows very nearly the same distribution of glycogen as does the normal individual.

The advent of insulin treatment is dispoiling the pathologist of the one opportunity for the positive postmortem diagnosis of active diabetes.¹⁶ The value of this means of histologic diagnosis is well shown by a recent case (No. 3928), where the diagnosis was established by the abnormal glycogen distribution. Miss A. P., aged sixty-nine years. Patient was supposed to have had mild diabetes, but diagnosis was never definitely established. In November, 1928, she developed left hemiplegia, and gradually grew worse, with mental deterioration. She showed no sugar in her urine, but this was presumably due to the low-caloric intake, which was little over that which would be allowed a moderately severe diabetic. Death occurred February 9, 1929, and an autopsy was performed three hours postmortem.

The chief cause of death was necrosis of cerebrum, secondary to arteriosclerosis. There was chronic pancreatitis, with sclerosis and hyalinization of the islands of Langerhans.

Best's carmine stain showed a slight amount of glycogen in the heart and voluntary muscle, a trace in the liver cells, much in the liver-cell nuclei, and a moderate amount in the epithelium of Henle's loops. On these findings, a diagnosis of diabetes mellitus was made.

The significance of the variation in glycogen content of the skin is as yet uncertain, but gives a reminder that this organ is by no means inconsiderable as a storehouse for glycogen. It is perhaps premature to attempt to correlate variations in cutaneous glycogen with the well-known susceptibility of the diabetic patient to cutaneous infections.

Conclusions. 1. Pathologic deposits of glycogen tend to disappear in insulin-treated cases of diabetes.

2. The normal storage of glycogen is increased in diabetic individuals by insulin treatment.

3. Sepsis decreases the effect of insulin so far as maintaining normal glycogen distribution is concerned.

4. The glycogen distribution may be a valuable aid in the post-mortem diagnosis of active diabetes.

5. Glycogen in the renal epithelium may represent an attempt at salvage of the carbohydrate being lost in the urine.

6. Variations in glycogen deposits in the skin of diabetics may be related to their susceptibility to cutaneous infection.

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EARLY CHANGES PRODUCED IN DOGS BY THE INJECTIONS OF A STERILE ACTIVE EXTRACT FROM THE ANTERIOR LOBE OF THE HYPOPHYSIS.

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IN a previous article¹ we have given the first account of Experimental Canine Acromegaly. In it we have shown the effects, on an English bull dog, of daily intraperitoneal injections of a sterile alkaline extract prepared from the anterior lobe of the hypophysis. It is the object of this paper to report on the early changes produced in dogs by such injections.

Experiment I. Two female foxhounds apparently thoroughbred littermates, were received on February 2, 1928. They were about four months old at that time, and resembled each other closely, as may be seen by the photograph taken March 19 (Fig. 1). On February 16, they weighed 3.9 and 3.6 kg. respectively. The heavier animal was reserved as a control, and the smaller one was given daily intraperitoneal injections of 15 to 20 cc. of sterile filtered anterior lobe extract.

The progress of their respective weights is shown by the chart (Fig. 2). The injected animal exceeded its control in weight within two weeks, and after three months of injections was approximately 50 per cent heavier.

The structural changes never became so marked as in the case of the injected English bull dog previously reported. The increase in height and weight was unmistakable, but not striking. The nose became long and thick, the skin loose and the abdomen protuberant. The paws became enlarged, and within two months of the beginning of injections, the animal became plantigrade instead of digitigrade (Figs. 3 and 4). The nipples became enlarged, but not the udders. There was no noticeable change in the vagina. Neither animal went into heat.

On May 23, it was noticed that the injected animal was losing weight and seemed sick. It died the next day, following administration of a purgative vermifuge.

Autopsy. Gross Findings. The cadaver was cold. Rigor mortis. Vomitus about the mouth. About 1 cm. of fat over the abdomen. Musculature well developed, and deep red in color.

The *thyroid* appeared somewhat enlarged. It was deep red in color, the acini plainly visible to the naked eye. There was a very large persistent *thymus* filling the entire superior mediastinum, and extending over the

pericardium to the diaphragm. The *heart* appeared normal. The *lungs* were injected, "downy" in consistency and free from pneumonic patches.

The *peritoneum* was full of a sanguineous fluid, perhaps 400 cc. in all. No source for it was found. The omentum contained much dark-green pigment, and the lymph glands were greatly enlarged. The *liver* was large, but appeared normal externally and on cut section. The *spleen* was large,

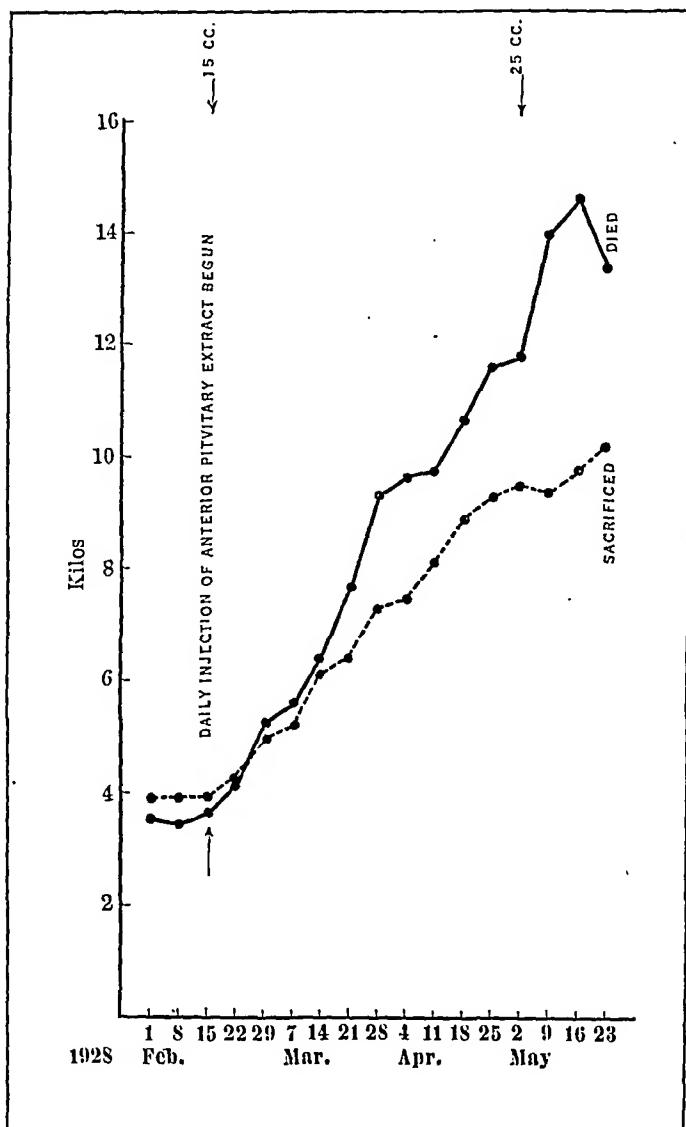


FIG. 2.—Chart of growth of the two animals. Weight in kilograms plotted at weekly intervals. The broken line indicates the control; the continuous line, the experimental animal.

soft and dark-blue in color. The *pancreas* appeared normal. The *kidneys* seemed perhaps a little enlarged. The *adrenals* were small. The *ovaries* and *uterus* were somewhat large for the age. There were neither large follicles nor corpora lutea in gross.

The *brain* was removed intact. It showed no gross abnormalities. The *hypophysis* appeared normal.

The control animal was sacrificed by etherization four days later. A complete autopsy was performed, but revealed no abnormalities. A comparison between the respective gross weights of the various organs in the two animals is given in Table I.

TABLE I.—FOXHOUNDS. COMPARATIVE WEIGHT OF ORGANS.

	Control hound, weight, gm.	Injected hound, weight, gm.	Increase in per cent.
Thyroid	1.50	3.000	100
Thymus	26.00	84.000	223
Heart	68.00	115.000	69
Liver	450.00	800.000	78
Spleen	21.00	42.000	100
Pancreas	28.00	45.000	60
Kidneys	56.00	136.000	143
Adrenals	0.75	1.000	25
Uterus	1.00	4.000	300
Ovaries	1.00	4.000	300
Brain	73.00	75.000	3
Hypophysis	0.07	0.075	7

Microscopic Findings. The *thyroid* of the injected animal already shows striking changes (Fig. 5). The cuboidal epithelium lining the glands is hypertrophied, thrown into folds, and is invading the lumen. There is an increase in the connective-tissue stroma as compared with that of the control animal. Whereas colloid is present in large amounts in the control, there is no colloid to be seen in the injected animal.

The *thymus* also shows a different structure in the two animals. The normal lobular arrangement seen in the control is very much less definite in the injected animal. There are fewer thymic corpuscles and fewer lymphocytes per high-power field in the injected animal. On the other hand, there is more fat and more edematous-tissue space.

Heart. No microscopic differences are noted between the two animals.

Lungs. Some of the alveoli in the injected animal are partly filled with a serous exudate. Those of the control are clear.

The *liver* shows certain quite definite changes, probably all attributable to the terminal infection (Fig. 6). There is a central necrosis which is hemorrhagic in character; in many areas there are fused hyaline masses of bloodclot. Throughout the sinuses there are more leukocytes present than in the control.

Neither the *spleen* nor the *pancreas* presents any microscopic differences in the two animals.

The *kidneys* show one very definite microscopic difference; namely, the glomeruli of the injected animal are unquestionably larger than are those of the control as established by comparing a large number of glomeruli under the oil-immersion lens. In the injected animal one glomerulus frequently extends beyond the limits of an oil-immersion field, whereas in the control no glomerulus can be found which quite fills the same field.

Adrenals. No microscopic differences are noted.

Uterus. Grossly this organ is four times the size of its control and microscopically the increase in size and development of muscular and endometrial tissue is very striking (Fig. 7).

Ovaries. The cells lining the follicles are elongated and columnar. In many places they have desquamated and filled the lumen. There is one irregular shaped cystic follicle containing an amorphous precipitate. There is some increase in the number of unripe follicles (Fig. 8).

Hypophysis. The anterior lobe appears to be edematous, with large intercellular spaces, but this may represent postmortem change. Otherwise the sections are similar in structure.

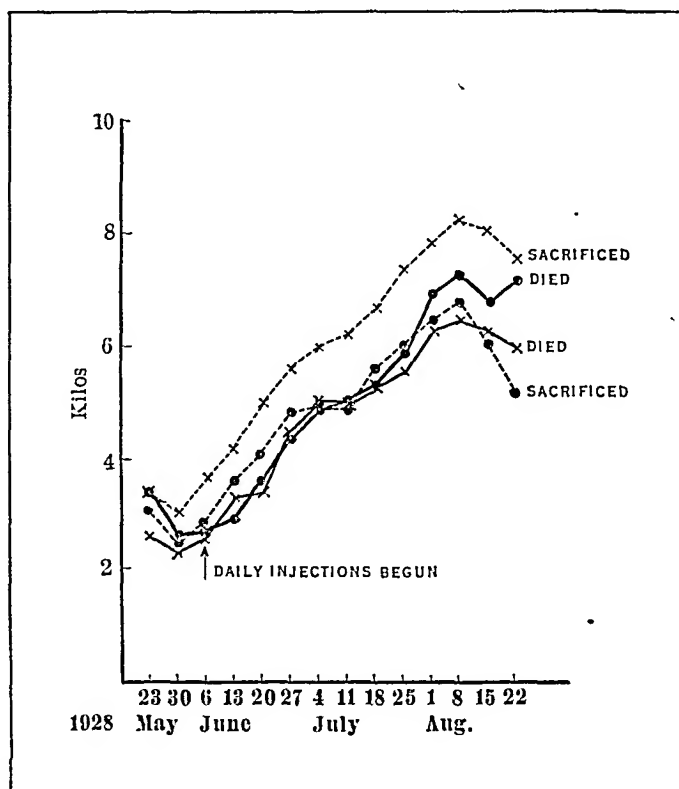


FIG. 10.—Chart of growth of the terriers. Weight in kilograms plotted at weekly intervals. The broken lines indicate the controls; the continuous line, the experimental animals. Disease and early death interfered with a satisfactory growth experiment.

Experiment II. Four female terriers, littermates resembling each other closely, were received in the laboratory on May 23, 1928, at which time they were ten weeks old (Fig. 9). They lived only three months longer, developing distemper in August, from which they died early in September. During their stay in the laboratory their progress was impaired by snuffles and minor upsets. After two weeks in the laboratory, daily injections of anterior-lobe extract were begun on the two smallest of the litter. Both became plantigrade about a month before their death. Their gain in weight is shown in the chart (Fig. 10). Disease and early death interfered with any appreciable increased rate of growth in the injected animals. Certain changes, however, had already taken place.

Autopsy. *Gross Findings.* One of the animals was not autopsied, as the body was in very poor condition, but a comparison of the weights of the organs of the other three is given in Table II. The striking feature is the enlargement of the heart and genital tract (Fig. 11) in the injected animal.



FIG. 1.—Littermate foxhounds on March 19, 1928, showing close resemblance early in experiment.

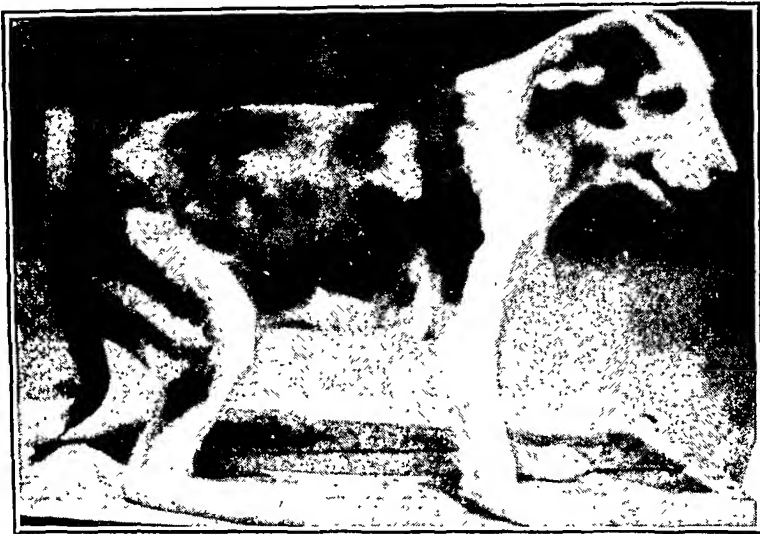


FIG. 3.—Experimental foxhound May 22, 1928, two months after injections were begun. Note plantigrade stance and inert attitude, contrasted with control (Fig. 4).



FIG. 4.—Control foxhound, May 22, 1928. Compare with Fig. 3

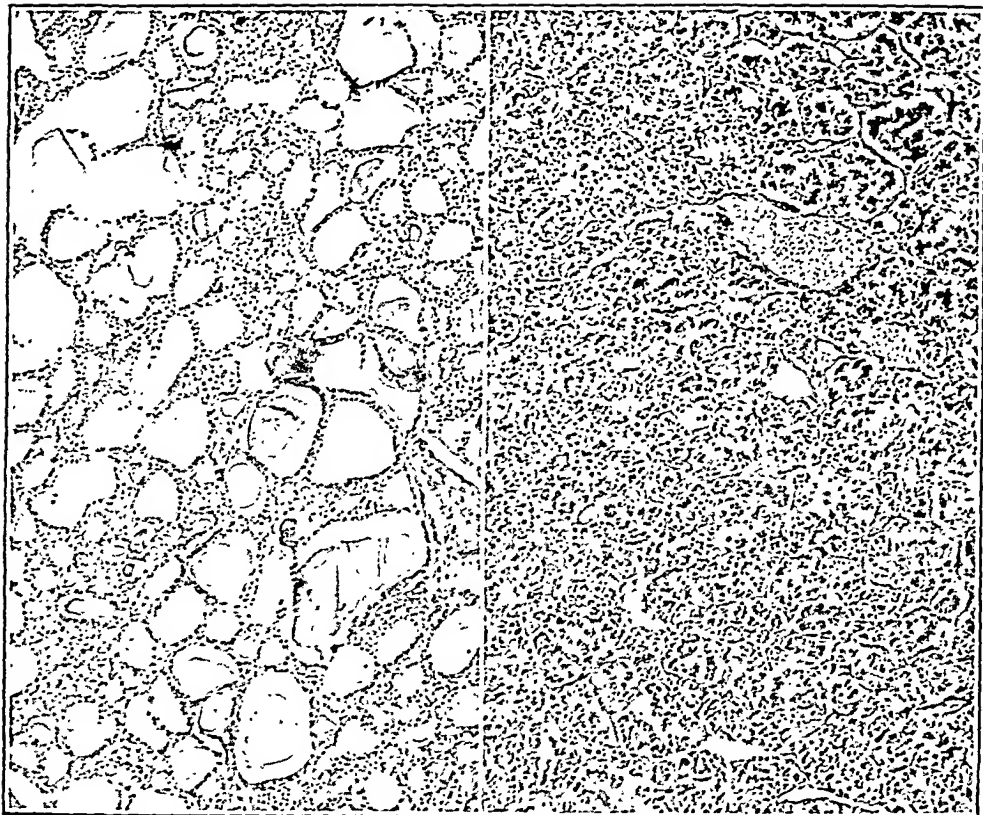


FIG. 5.—Thyroids: Control, left; experimental animal, right. Note hypertrophied epithelium, collapsed alveoli, and absence of colloid in the experimental animal: $\times 80$.

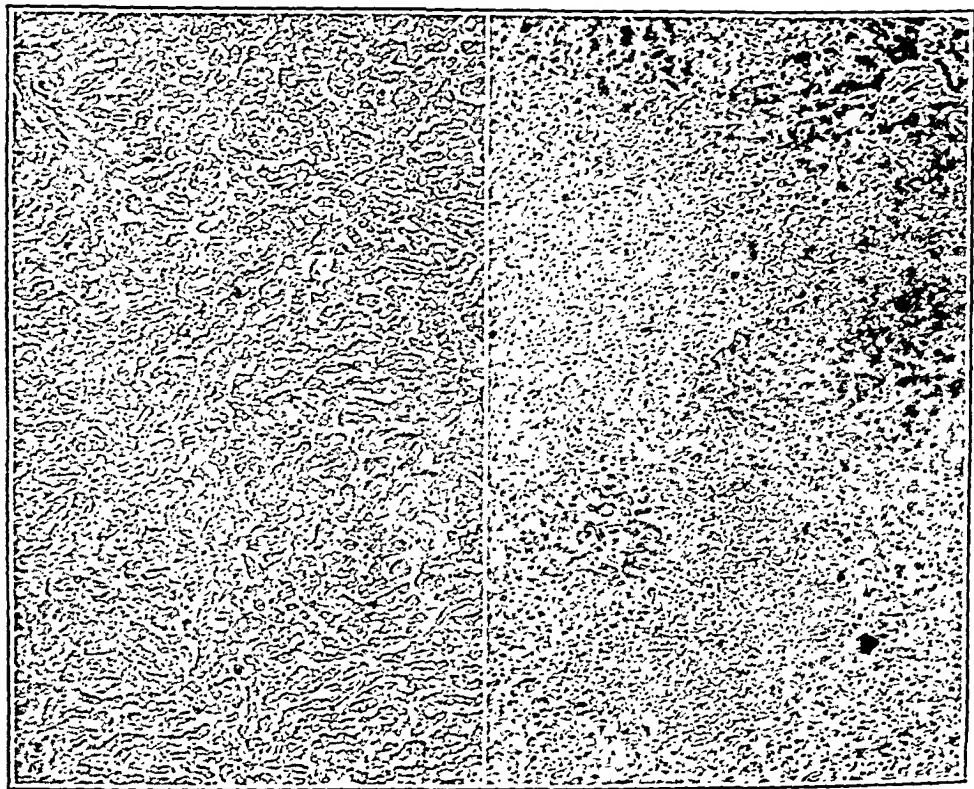


FIG. 6.—Liver: Control, left; experimental animal, right. Note necrotic areas, and leukocytic infiltration. $\times 80$.

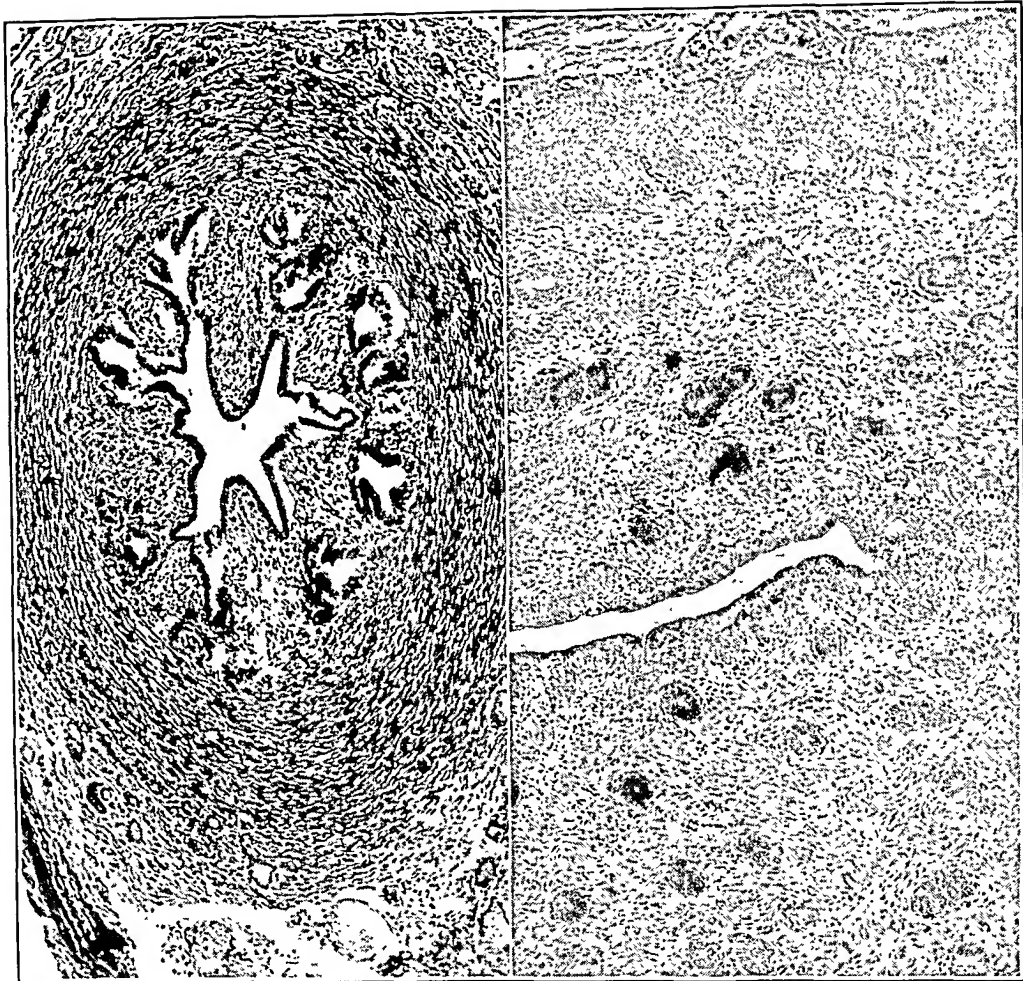


FIG. 7.—Uterus: Control, left; experimental animal, right. Note extreme difference in size and development. $\times 80$.

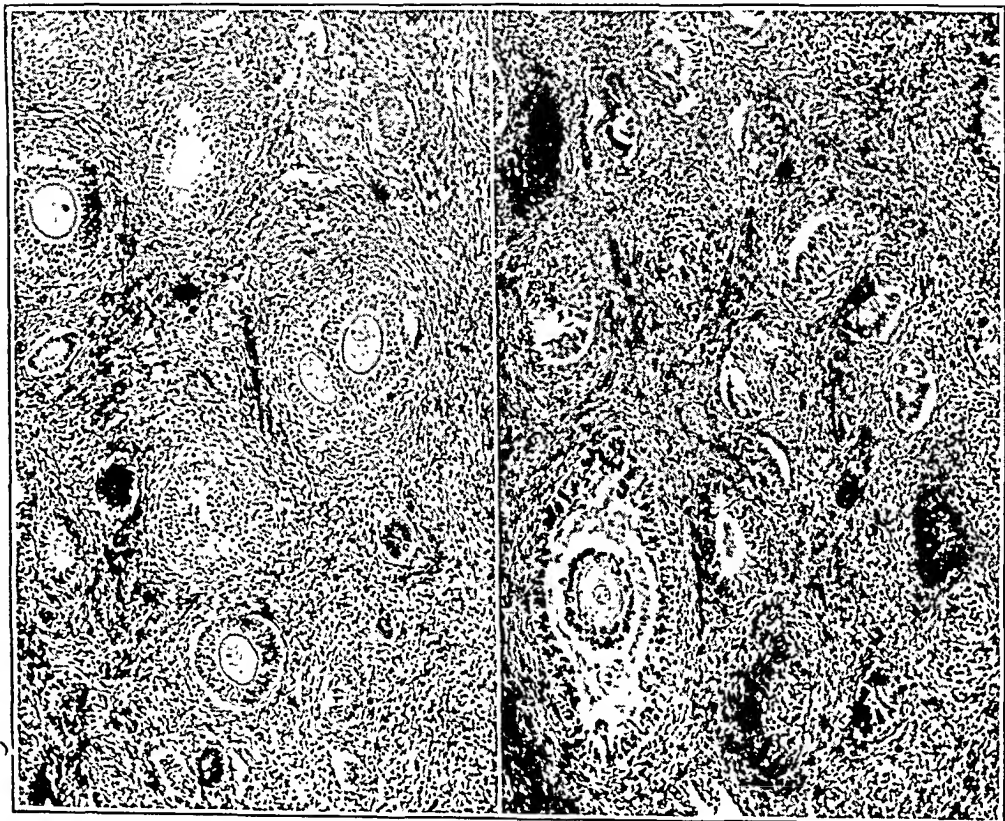


FIG. 8.—Ovary: Control, left; experimental animal, right. Note that there are no normal follicles in the experimental animal. $\times 80$.



FIG. 9.—Littermate terriers when first received, May 30, 1928.

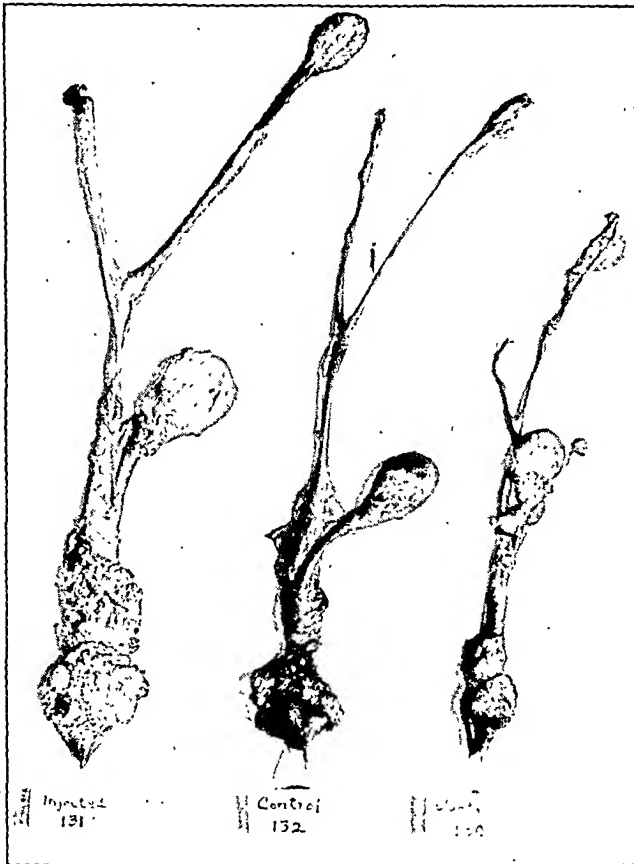


FIG. 11.—Terriers. Photograph showing comparative size and development of genital tracts.



FIG. 13.—Collies, one week after shaving band of hair. Control animal on left shows hair already growing. Hypophysectomized animal on right shows almost no growth of hair.

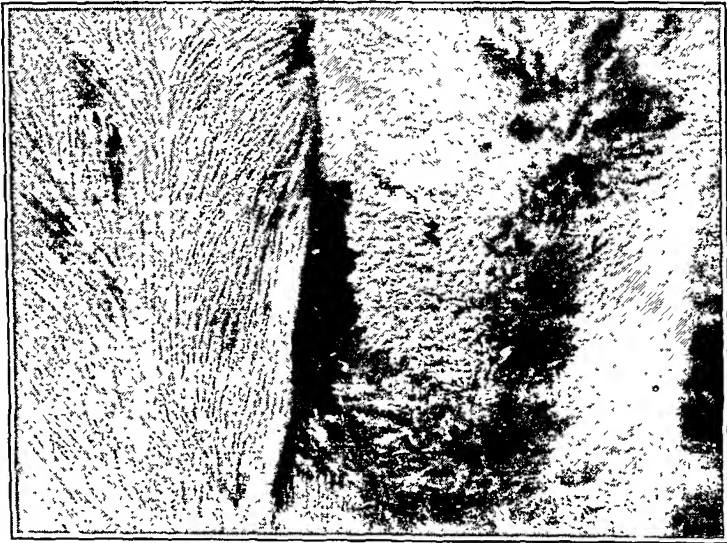


FIG. 14.—Collies, two months after shaving band of hair. Control animal on right shows hair entirely grown. Hypophysectomized animal on left shows slight growth of hair with band still plainly visible.



FIG. 15.—Smallest hypophysectomized collie, showing liveliness two months after operation.



FIG. 16.—Smaller hypophysectomized collie with control, two months after operation.

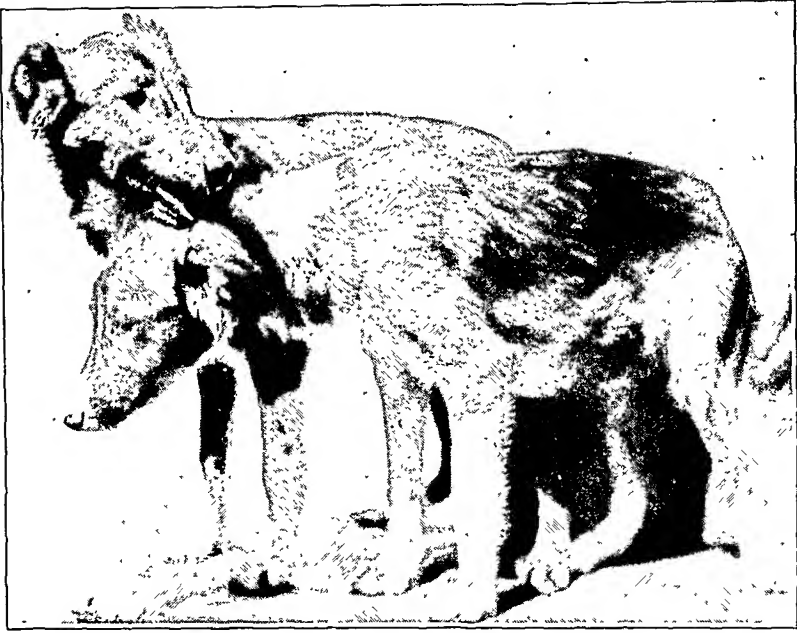


FIG. 17.—Collies. Injected animal in front. Control, behind. Note early plantigrade position and general lack of interest of injected animal.

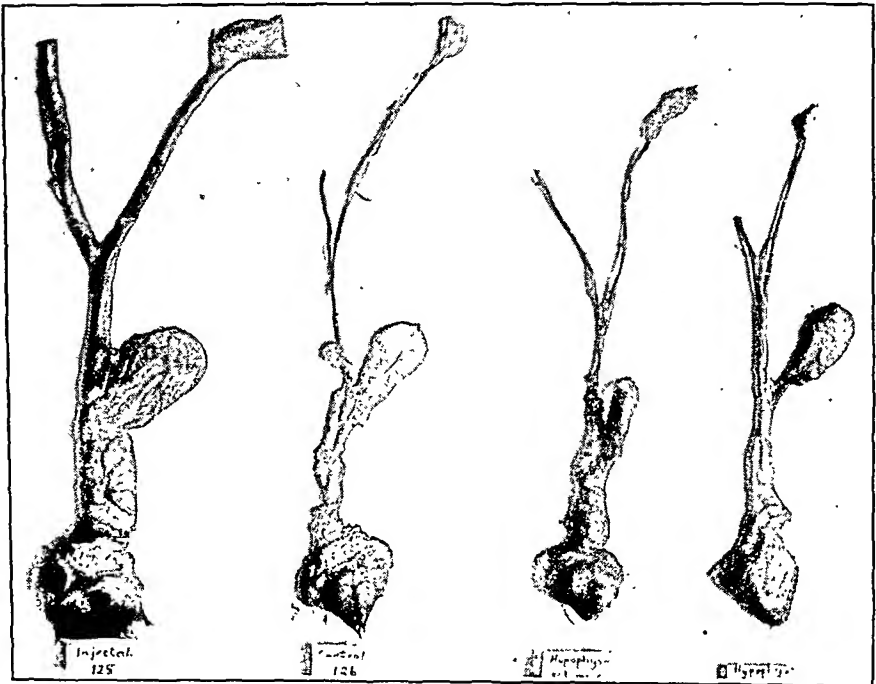


FIG. 18.—Photograph to show comparative size of genital tract in the four collies. Note how much larger is that of the injected animal on the left.

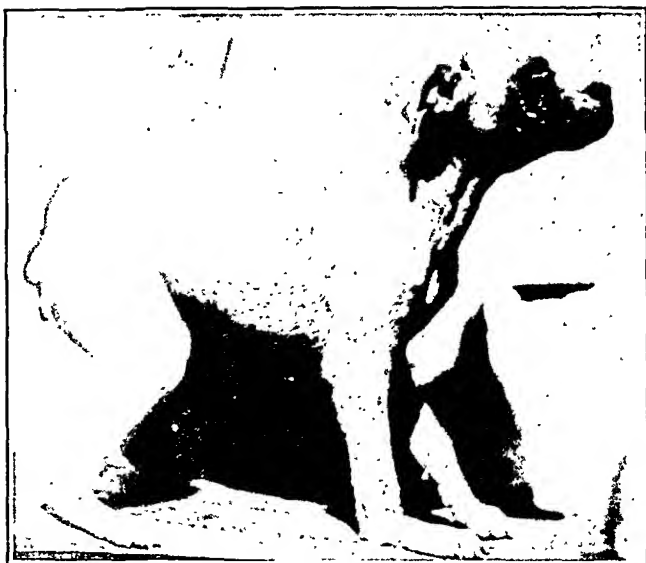


FIG. 19.—Male terrier after two months of injection, showing general weakness and plantigrade stance.

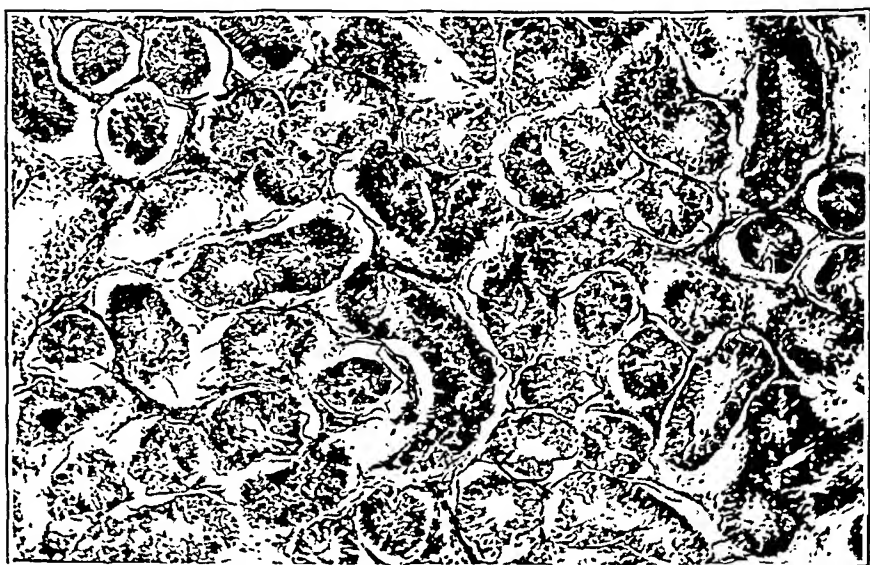


FIG. 20.—Testicle: showing degenerate structure with tissue invading the central portion of the tubules. $\times 80$.

Whereas the other organs are smaller in the injected animal than in the larger control, the heart and genital tract are noticeably larger—the heart more than a third again as large, and the genital tract more than two and a half times as large.

TABLE II.—TERRIERS. COMPARATIVE WEIGHT OF ORGANS.

	Control.	Injected.	Control.
Thyroid	5.00	2	1.50
Heart	75.00	105	44.00
Liver	600.00	463	340.00
Spleen	28.00	23	23.00
Pancreas	32.00	?	12.00
Kidneys	84.00	66	62.00
Adrenals	4	3	2.00
Genital tract	24.00	63	19.00
Brain	72.00	70	68.00
Length of intestine in meters	4.82	4	4.18

Microscopic Findings. Certain changes are to be noted even at this early date. The *thyroid* of the injected animal shows an absence of colloid whereas there is abundant colloid present in the control. The acini are in many places filled with débris which proves to be degenerated cells. The secreting cells are thrown into folds in some places as occurs typically in exophthalmic goiter, appearing also to be individually larger and more columnar in character than corresponding cells in the control section, which are relatively flat or cuboidal.

The *kidney* also shows the changes in the glomeruli noted in the previous experiment—namely, the actual size of the glomerulus of the injected animal is larger than the glomerulus of the control, as measured by comparison of each in the oil-immersion field.

Uterus. The walls are very much thickened and there is a considerable increase in endometrial tissue over that seen in the control. The appearance is similar to that shown in Fig. 7 (previous experiment).

Ovaries. In the injected specimen there is a very considerable increase in the number of follicles.

The sections from other organs do not present any definite change from the normal histology.

Experiment III. Four collies, littermate sisters, apparently purebred animals, were received in the laboratory on May 2, 1928, at which time they were two months old. They lived four months more, dying or being sacrificed because of respiratory infection.

Two of the animals were completely hypophysectomized at the end of two weeks in the laboratory. Hypophysectomy was performed by the usual temporal route and the gland removed by suction. One animal was reserved as a control and the remaining one used for injections of anterior-lobe extract. The progress of these four animals in regard to gain in weight is shown in the accompanying chart (Fig. 12). It is evident that the two hypophysectomized animals stopped gaining weight about one month postoperative. Both the other animals continued to gain in an apparently normal manner, the injected animal gaining on the whole somewhat faster than the control, so that the former, although somewhat

lighter than the latter originally, was slightly heavier at the time of death.

Observations were made in these animals regarding the growth of hair. After they had been in the laboratory about three weeks a wide band of hair, completely circling the trunk in its midportion, was shaved, and the progress of the new growth of hair was carefully noted (Fig. 13). Two months after shaving, both the hypophysectomized animals showed the band very plainly (Fig. 14), and in

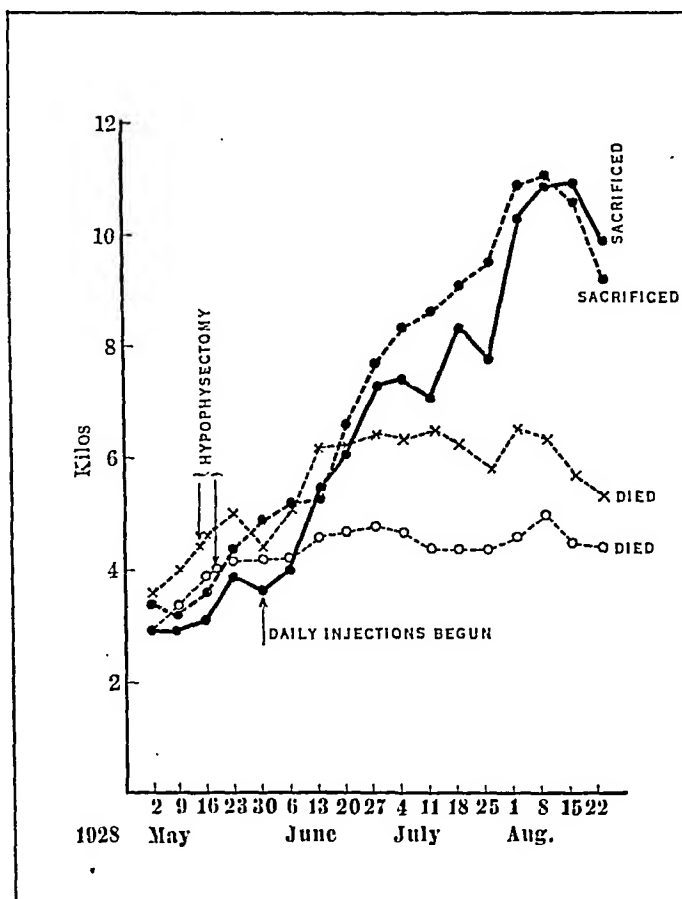


FIG. 12.—Chart of growth of the collies. Weight in kilograms plotted at weekly intervals. The continuous line indicates the injected animal; the broken line, the control; the two dotted lines, the hypophysectomized animals.

one of them there had been practically no growth of hair at all. In the control and the injected animals on the other hand, the hair had again become of normal length, there being no band visible. These findings coincide with our previous observations in this laboratory.² It is also interesting to note the liveliness of the operated and control animals as compared with the injected animal (Fig. 15). A comparison of the size and general appearance of three of the animals is given in the photographs (Figs. 16 and 17).

At the end of four months the two operated animals developed upper respiratory infection from which they died. The other two were also in poor condition and both losing weight. They were, therefore, sacrificed at the same time.

Autopsy. Gross Findings. The control animal showed very little of note except for slight bronchopneumonia and marked tracheitis.

The injected animal showed some abnormalities. There was slight prognathism and evident enlargement of the heart and genital tract (Fig. 18).

The Smaller Hypophysectomized Animal. Subsequent microscopic examination showed that not quite all the anterior lobe was removed at operation; however, very little anterior-lobe tissue remained, and clinically there was almost complete cessation of growth. It was noted that the jaw was receding in character. The thyroid seemed particularly pale. The lungs showed definite bronchopneumonia. All the other organs appeared small, especially the uterus, tubes and ovaries.

The Larger Hypophysectomized Animal. In this case microscopic examination showed the operation to have been complete—no hypophyseal tissue remained. Here again the thyroid appeared pale. Otherwise the gross examination was not remarkable.

A comparison of the weights of the organs is given in Table III.

TABLE III.—COLLIES. COMPARATIVE WEIGHT OF ORGANS.

	Small ectomized.	Large ectomized.	Control	Injected.
Thyroid	1.00	?	1.00	2.00
Heart	40.00	47.00	98.00	112.00
Liver	250.00	80.00	750.00	700.00
Spleen	8.00	?	28.00	26.00
Pancreas	12.00	18.00	36.00	55.00
Kidneys	35.00	55.00	92.00	112.00
Adrenals	0.50	?	3.00	1.50
Genital tract	13.00	20.00	28.00	37.00
Brain	60.00	?	?	66.00
Length of intestine, meters	3.54	3.07	4.61	4.67

Microscopic Findings. Thyroid. The control animal shows normal structure and normal blue staining colloid present in the usual amounts (all sections stained with hematoxylin and eosin).

The injected animal shows the presence in some of the acini of moderate amounts of pink-staining colloid but many acini are filled with a cellular and amorphous débris. The epithelium lining the glands is hypertrophied, tending to be columnar in type and to invade the lumen in many places. There is an excessive amount of interglandular connective-tissue stroma.

The thyroid glands of the two hypophysectomized animals do not show any abnormality.

Heart. There are no unusual findings in any of the sections.

Liver. The only pathology noted in this organ was in the smaller hypophysectomized animal in which there were areas of central necrosis with fat infiltration into the trabeculae.

Spleen and Pancreas. Sections from these organs all show essentially normal histology.

Kidneys. The glomeruli of the injected animal are already definitely larger than are those of the control or of the operated animals. There is no appreciable difference in size, however, between the glomeruli of the control as compared with the operated animals. In other respects the histology is not remarkable.

Adrenals. The adrenal glands show no definite abnormalities.

Uterus. There appears to be an unusually large amount of endometrial and connective tissue in the injected specimen and relatively little in the larger hypophysectomized specimen. The uterus of the smaller operated animal is very small and immature.

Ovaries. The ovary of the injected animal shows an increase in the number of unripe follicles but no ripening eggs. The ovary of the smaller hypophysectomized dog is particularly small and contains few follicles, none of which are mature.

Hypophysis. There are no microscopic changes seen. Serial sections through the hypophyseal region in the smaller operated animal show minute amounts of anterior hypophyseal tissue remaining. Similar serial sections in the larger operated animal show that hypophysectomy was complete. There is no evidence of injury to the floor of the third ventricle.

Experiment IV. A further experiment concerns the effect of injecting the anterior lobe extract in a male dog.

On February 2, 1928, we received in the laboratory a litter of 6 terriers, 3 males and 3 females. Unfortunately, 5 of them developed distemper and died before any noteworthy changes developed. One male, however, lived seven months in the laboratory, being received at the age of about two months and dying at the age of about nine months. Daily injections of 15 to 30 cc. of sterile anterior-lobe extract were carried out during the last three and a half months. After two months of injection the animal became markedly plantigrade (Fig. 19).

Autopsy. *Gross Findings.* *Jaw.* Well-marked prognathism was noted.

Thyroid. This organ was somewhat enlarged, red and hyaline in character.

The *thymus* was not identified.

The *lungs* showed bronchopneumonia.

The *liver* appeared unduly large (800 gm.) with particularly prominent architecture.

The *adrenal cortex* was slightly thickened and the medulla unusually pink.

The *testicles* were small.

Otherwise the organs were negative.

Microscopic Findings. The only organs presenting abnormalities were the thyroid and genitalia.

The *thyroid*. Some of the acini here are filled with cellular debris. There is an abnormally small amount of colloid in the cells and in the acini. The cells lining the acini are cuboidal.

Testicle. No sexual cells can be found which have developed beyond the spermatocyte stage. The central portion of the tubules is occupied by strands of degenerate tissue (Fig. 20).

Epididymis. The cells lining the ducts are cuboidal and possess no cilia.

Penis. This organ resembles that of an immature animal and contains little erectile tissue.

Summary and Conclusion. The experiments reported here confirm our earlier observations on experimental hyperpituitarism and show particularly the early changes resulting from daily injection of a sterile active anterior-lobe extract.

After only three months of injection there are noted very definite changes in the thyroid gland and in the genital tract.

The changes in the thyroid consist in hypertrophy of the gland epithelium with invasion of the lumen and almost complete absence of colloid.

As to the genital tract, both male and female were sexually inactive. In the female there is an hypertrophy of the uterus, ovaries and vagina. In the male there is no hypertrophy, the testicles being small and showing only the earliest stages of spermatogenesis.

Skeletal overgrowth and splanchnomegaly were noticeable in the case of the foxhounds after three months of injection.

Sluggishness, inalertness and plantigrade stance were all noted after two months of injection.

A comparison was made between hypophysectomized and normal animals. Cessation of growth after hypophysectomy was confirmed. A marked slowing in the rate of growth of hair was noted. Normal alertness was not interfered with by hypophysectomy.

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THE DIFFUSIBILITY OF CALCIUM IN BRONCHIAL ASTHMA AND ALLIED DISORDERS, AND IN PULMONARY TUBERCULOSIS.

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BRONCHIAL asthma has been studied from many angles. At the present time there is no single factor which can be regarded as responsible for the paroxysms. As stated by Pottenger,¹ "the underlying reacting capacity of the individual's bronchial neuromuscular mechanism must be taken into consideration as well as the exciting cause. . . . When all the facts are carefully weighed the argument seems strongly supported that there is something in the make-up of the asthmatic patient which makes him susceptible to the action of proteins, climatic change, and physical and chemical irritants." The nature of the tissue state which constitutes the basis for this susceptibility is not known. Many theories have been advanced, among which is that of calcium deficiency.

The elaboration of this theory is dependent upon certain physiologic and pharmacologic facts and upon clinical observation, but it has not been supported by any substantial experimental evidence. From a physiologic viewpoint, the asthmatic paroxysm may be considered a condition of local vagotonia, as suggested by Eppinger and Hess.² In the light of our present knowledge of the vegetative nervous system and its functional interrelationships, vagotonia must be interpreted in a broader sense than as merely a disturbance of autonomic nervous balance. Ringer³ many years ago demonstrated the pharmacologic antagonism of calcium and sodium and potassium, and showed that a proper balance between these elements is necessary for the preservation of normal cardiac function. More recent studies by Howell and Duke,⁴ Kolm and Pick,⁵ Kraus and Zondek,⁶ Andrus and Carter,⁷ Loewi,⁸ Petersen⁹ and many others have established the relationship between autonomic balance and the ratio of calcium to sodium and potassium in the tissues. These studies indicate that vagotonia (parasympathicotonia) is associated with a diminished calcium-potassium and calcium-sodium ratio. This suggested relative or actual calcium deficiency has been assumed by some as a logical basis for calcium therapy in bronchial asthma and allied disorders.

This assumption has met with vigorous opposition because of the fact that a calcium deficiency has not been satisfactorily demonstrated in these conditions. Practically all of the experimental studies in this connection, at least in human beings, have concerned themselves with the determination of the calcium content of blood serum. A recent study by Crip and McElroy¹⁰ of 167 cases of atopy, including asthma, hay fever, vasomotor rhinitis, urticaria and angioneurotic edema showed the level of serum calcium to be within normal limits in the great majority of instances, a few being slightly below and above normal. Greenbaum,¹¹ in a study of 63 patients with urticaria, found normal or elevated serum calcium values in all but one. Schamberg and Brown¹² and Schwartz and Levin¹³ reported similar negative findings. Novak and Hollander¹⁴ found a suggestive diminution in serum calcium in vasomotor rhinitis but not in hay fever and asthma, while Sonnenschein and Pearlman¹⁵ reported normal findings in vasomotor rhinitis. There is some contradictory evidence which, however, does not seem very convincing. For example, Brown and Hunter,¹⁶ regarding any figure below 9.6 mg. as subnormal, believe that a calcium deficiency exists in a large proportion of all patients with atopic disorders. It must apparently be concluded that the bulk of evidence points to the fact that in the great majority of such cases the blood-serum calcium is within normal limits.

In spite of these findings, calcium salts are extensively employed in the treatment of bronchial asthma, urticaria and allied conditions. There can be no doubt that such therapy is of distinct benefit in

many cases. Because of the normal serum calcium values, it is believed by most workers in this field that the clinical improvement is due to the depressing action of calcium and to its inhibiting influence upon cell permeability. A few, however, still maintain that there may be a disturbance of calcium balance not readily demonstrable by ordinary means. Hanzlik,¹⁷ in a review of the problem of allergy, states that calcium salts prevent or inhibit experimental edema and clinical allergic manifestations, owing presumably to their power to lessen cellular permeability, indicating indirectly therefore the possible physical basis for the reactions produced by many agents.

Until modern chemical methods made possible more exact studies of mineral balance, many believed that pulmonary tuberculosis was associated with a process of demineralization. At the present time, however, there is no evidence to support this theory; no significant decrease in the calcium content of blood or tissues has been demonstrated and no increase in calcification of tuberculous lesions has been found after calcium administration. The subject has been reviewed by Wells¹⁸ and by Gordon and the writer.¹⁹ Since the early studies of von Pirquet,²⁰ the relation of the allergic state to reinfection in tuberculosis has been thoroughly investigated. There seems to be no doubt that the "second infection" or "adult type" of pulmonary tuberculosis is characterized by a preëxisting and co-existing state of hypersensitiveness to the tubercle bacillus and its products. Therefore, from this standpoint, the pathologic physiology of the tissues in "adult" pulmonary tuberculosis and in bronchial asthma should have certain features in common. If a disturbance of calcium balance is an essential feature of allergic disorders it should likewise exist in this form of tuberculosis. As stated previously no calcium deficiency has been demonstrated. Halverson, Mohler and Bergeim²¹ and Sweany, Weathers and McClusky²² have found the serum calcium in most patients with tuberculosis to be within normal limits, and furthermore, there seems to be no constant relationship between the blood-calcium level and the extent or activity of the pulmonary lesion.

It may be quite definitely asserted that in the great majority of patients with some manifestation of allergy or hypersensitiveness the serum calcium is within normal limits. This fact, however, does not of itself justify the conclusion that there is no disturbance of calcium balance in these conditions. The subject of calcium metabolism is quite involved and there is still much to be learned concerning it, but certain facts have been rather definitely established. An understanding of the condition of calcium in the blood and tissues is essential to the proper appreciation of the manner in which the calcium balance may be disturbed in disease.

The normal serum calcium concentration is from 9 to 11 mg. per 100 cc. Physiologically this exists in two states, termed diffusible

and nondiffusible. The diffusible fraction is that portion which is capable of passing through the capillary walls and cell membranes; the nondiffusible normally cannot, being bound in some way, it is believed, to the serum proteins. In a previous study²³ the normal figures for diffusible calcium were found to be 4.5 to 5.5 mg. per 100 cc., those for nondiffusible calcium being 4.7 to 5.75 mg. per 100 cc. In addition, a portion, estimated at about 20 per cent of the total, probably exists in ionized form, the remainder being unionized. These facts are obviously of great importance for the pharmacologic properties of the various calcium states must be quite different. The production of a calcium effect is dependent not so much upon the level of calcium in the blood as upon its distribution in the blood and tissues. This may perhaps be best expressed by the ratio of the diffusible to the nondiffusible, and of the ionized to the unionized fractions, the latter of which cannot be satisfactorily determined by present methods. These points may be illustrated by the following equation:

$$\begin{array}{rcl}
 \text{Total serum calcium} & = & \text{Diffusible calcium} + \text{Nondiffusible calcium} \\
 9 \text{ to } 11 \text{ mg.} & & \begin{array}{l} 4.5 \text{ to } 5.5 \text{ mg.} \\ (1) \text{ Ionized } 2 \text{ mg.} \\ (2) \text{ Unionized} \end{array} + \begin{array}{l} 4.7 \text{ to } 5.75 \text{ mg.} \\ \text{Unionized} \end{array}
 \end{array}$$

It can readily be seen that alterations in these ratios may occur without any change in the amount of serum calcium.

The maintenance of the normal calcium balance is dependent upon many factors, among which are the nature and amount of serum proteins, the parathyroid hormone, the concentration of phosphate and carbonate ions and the hydrogen-ion concentration. The manner in which these factors operate cannot be gone into, but there is no question of the occurrence of disturbances of calcium balance as indicated by alterations in the proportions of the diffusible and the ionized fractions, the total serum calcium being within normal limits. For example, in certain forms of tetany dependent upon a condition of alkalosis, the serum calcium level is often normal, the symptoms being due to a diminution in the proportion of ionized calcium. Then too, in jaundice there is some disturbance of the availability or utilization of calcium, although the serum calcium level may be normal or above normal. This is illustrated by the studies of Bowler and Walters²⁴ and of Dodek, Gordon and the writer.²⁵ The point of special significance in connection with the present study is the fact that the amount of serum calcium is not always a true index of the state of the calcium balance.

The vital importance of the preservation of the normal calcium distribution is probably due, in a large degree, to the influence of this element upon the permeability of the cell membrane. The functional activity of the cell depends upon the exchange of material between its interior and exterior, the permeability of the cell membrane being the determining factor in this exchange. It is well

recognized and readily demonstrable that normal permeability is dependent to a considerable extent upon the presence of a normal balance between the inorganic ions in the fluid bathing the cell. Calcium diminishes cell permeability; in fact, Loeb²⁶ attributes the general inhibiting action of calcium to this property. The possible significance of this fact in connection with the problem of hypersensitiveness is apparent in the light of the observations of many investigators summed up in the statement by Manwaring,²⁷ that increased capillary permeability will ultimately be found to be the dominant fundamental characteristic of protein sensitization and anaphylaxis. It is of interest to note that Petersen⁹ found abnormal degrees of permeability of skin capillaries in patients with pulmonary tuberculosis. The possible relation of this observation to the hypersensitive state of the tissues in tuberculosis is a point worthy of consideration.

Present Investigation. The present investigation consists of the determination of the diffusibility of calcium in 25 patients with bronchial asthma, 3 with mucous colitis, 2 with vasomotor rhinitis, 1 with angioneurotic edema and 63 with pulmonary tuberculosis.

Method. There are two ways in which the diffusibility of calcium may be estimated: (1) by ultrafiltration or dialysis through an artificial membrane; (2) by the determination of the calcium content of cerebrospinal fluid. Under normal conditions the figures obtained by the two methods are practically identical. It must be realized, however, that the diffusibility of calcium in the body is dependent upon two variable factors; namely, the condition of calcium in the blood stream and the permeability of the capillary walls and cell membranes. When ultrafiltration or dialysis is employed the latter factor is disregarded, a fact which is of particular importance in connection with the conditions under consideration since it is believed that they are associated with or dependent upon an increase in cell permeability. This has been discussed more fully in a previous communication.²³ The method employed in this study consists in the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case. The calcium determinations were made by the Clark-Collip modification of the Kramer-Tisdall procedure.²⁸ The spinal fluid calcium is termed diffusible although "diffused" is probably more correct. The difference between this figure and the total serum calcium is the nondiffusible portion.

The pertinent data are presented in the accompanying tables.

Discussion. Atopic Disorders. The serum calcium in this series ranged from 7 to 12.67 mg. per 100 cc., 6 being below 9 mg. and 2 above 11 mg. per 100 cc. The detailed findings are presented in Table I. In a previous study²³ the normal cerebrospinal fluid calcium concentration was found to be from 4.50 to 5.50 mg. and the nondiffusible from 4.7 to 5.75 mg. per 100 cc., the ratio of

diffusible to nondiffusible calcium being 82 to 115 per cent. In the group of patients with atopic disorders the spinal fluid calcium ranged from 4.39 to 6.33 mg. per 100 cc., 20 being above and 1 below normal. The nondiffusible calcium varied between 1.5 and 7.5 mg., 2 being above and 22 below normal. The ratio of diffusible to nondiffusible calcium was from 68.9 to 400 per cent, 23 being above and 2 below normal.

TABLE I.—THE TOTAL SERUM CALCIUM, THE DIFFUSIBLE AND NON-DIFFUSIBLE CALCIUM, AND THE RATIO OF DIFFUSIBLE TO NON-DIFFUSIBLE CALCIUM IN 31 PATIENTS WITH ATOPIC DISORDERS AND 63 WITH PULMONARY TUBERCULOSIS.

Condition.	Cases.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, diffusible to nondiffusible.*
Asthma	25	7.00 to 12.67	4.39 to 6.33	1.50 to 7.50	68.9 to 400
Mucous colitis	3	9.84 to 11.00	5.62 to 6.00	4.22 to 5.00	120 to 133
Vasomotor rhinitis	2	10.55 to 10.70	5.75 to 6.10	4.45 to 5.00	115 to 137
Angioneurotic edema	1	8.2	5.5	2.7	203
Pulmonary tuberculosis	63	8.10 to 13.80	4.00 to 7.75	3.34 to 8.87	56.7 to 152

* Calcium values expressed in mg. per 100 cc. Ratios expressed as percentage.

There are factors other than the diffusibility of calcium which may influence its concentration in the cerebrospinal fluid. One of these is an inflammatory condition of the brain or meninges. This was present in no instance in this series. It is also theoretically possible that the level of calcium in the spinal fluid may be altered by changes in the intracranial venous and arterial pressures resulting in variations in the filtration of constituents of the blood plasma into the subarachnoid space. If this factor is operative the concentration of other poorly diffusible constituents of the spinal fluid, such as glucose, should be correspondingly altered. Glucose determinations were carried out in 18 of the 25 patients with bronchial asthma. The blood sugar varied from 86 to 102 mg., and the spinal fluid sugar from 46 to 56 mg. per 100 cc., showing no evidence of increased filtration pressure. The increase in the level of calcium in the cerebrospinal fluid is in all likelihood, therefore, dependent upon one or both of two conditions: (1) an actual increase in the diffusibility of serum calcium; (2) a selective increase in the permeability of the cell membranes and capillary walls. Since there is no indication in this group of cases of any locally operating factor in the brain, cord or meninges, these observations may be postulated as being representative of conditions existing throughout the tissues.

These findings seem to be indicative of a state of increased calcium diffusibility in atopic disorders. There has been very little investi-

gation of this problem. Blum, Delaville and Caulaert²⁹ found an increase in diffusible calcium in the rabbit and the dog during peptone shock. Brown and Ramsdell³⁰ studied the diffusibility of calcium in anaphylactic shock in guinea-pigs by the artificial membrane method. In the shocked animals there was a considerable increase in the diffusible fraction of serum calcium, the total calcium being essentially unaltered. Similar changes were observed following the administration of histamin. These observations coincide with our findings in bronchial asthma and allied disorders. The exact significance of this state of increased calcium diffusibility is a matter for conjecture. However, in view of the intimate relationship between cell permeability and inorganic-ion balance these observations appear to be of fundamental importance.

Pulmonary Tuberculosis. The serum calcium values in the group of 63 patients with pulmonary tuberculosis varied from 8.10 to 13.80 mg. per 100 cc., 17 being above 11 mg. and 2 below 9 mg. The cases have been divided into 3 groups accordingly as the ratio of diffusible to nondiffusible calcium was normal, increased or decreased. The abnormal findings are presented in Tables II and III.

TABLE II.—SIXTEEN CASES OF PULMONARY TUBERCULOSIS WITH RATIO OF DIFFUSIBLE TO NONDIFFUSIBLE CALCIUM ABOVE NORMAL.

Case.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, diffusible to nondiffusible.*	Lesion.
6 . . .	10.29	5.88	4.41	133	Exudative; advanced.
9 . . .	8.50	5.00	3.50	142	Exudative; advanced.
11 . . .	10.00	5.50	4.50	122	Proliferative; active.
17 . . .	8.10	4.76	3.34	142	Exudative; advanced.
18 . . .	10.00	5.71	4.29	133	Exudative; advanced.
21 . . .	10.00	5.71	4.29	133	Exudative; advanced.
23 . . .	9.52	5.28	4.24	125	Exudative; advanced.
25 . . .	10.56	5.85	4.71	124	Exudative; advanced.
28 . . .	10.56	6.13	4.43	138	Exudative; advanced.
37 . . .	9.38	5.67	3.71	152	Exudative; dying.
53 . . .	10.00	5.75	4.25	135	Exudative; advanced.
55 . . .	10.50	5.75	4.75	121	Exudative; advanced.
59 . . .	11.57	6.48	5.09	127	Exudative; advanced.
77 . . .	13.00	7.75	5.25	128	Exudative; advanced.
104 . . .	9.36	5.61	3.75	147	Exudative; dying.
114 . . .	8.63	4.65	3.98	117	Exudative; dying.

* Calcium values expressed in mg. per 100 cc. Ratio expressed as percentage.

In 16 patients the diffusibility ratio was from 117 to 152 per cent as contrasted with the normal range of 82 to 115 per cent. With one exception, (Case 11), the lesions, by Roentgen ray examination,

were of the exudative type, in an advanced stage. All were clinically active and 4 in a critical condition.

In 11 patients the diffusibility ratio was from 56.7 to 80.1 per cent. In each case the lesion was of the proliferative or fibroid types, 3 of the patients showing evidence of advanced peripheral arteriosclerosis. In 3 instances the process was quiescent and no one in this group was critically ill.

The 36 patients with diffusibility ratios within normal limits presented no constant clinical features. All were suffering with chronic ulcerative tuberculosis in varying stages of activity. In this group there appeared to be no correlation between the calcium distribution and the nature or extent of the pulmonary lesion.

TABLE III.—ELEVEN CASES OF PULMONARY TUBERCULOSIS WITH RATIO OF DIFFUSIBLE TO NONDIFFUSIBLE CALCIUM BELOW NORMAL.

Case.	Serum.*	Diffusible.*	Nondiffusible.*	Ratio, Diffusible to nondiffusible.*	Lesion.
12 . .	11.50	5.00	6.50	76.9	Proliferative.
27 . .	11.32	4.71	6.61	71.2	Proliferative; quiescent.
38 . .	13.80	4.93	8.87	56.7	Proliferative arteriosclerosis.
54 . .	11.50	5.00	6.50	76.9	Fibroid tuberculosis.
76 . .	10.50	4.00	6.50	61.5	Fibroid arteriosclerosis.
81 . .	12.68	4.87	7.81	62.3	Fibroid arteriosclerosis.
96 . .	9.55	4.25	5.30	80.1	Proliferative.
97 . .	9.60	4.20	5.40	77.7	Proliferative; quiescent.
102 . .	12.19	4.87	7.32	66.5	Fibroid; arteriosclerosis.
103 . .	12.19	4.87	7.32	66.5	Proliferative; quiescent.
105 . .	10.72	4.65	6.07	76.6	Fibroid tuberculosis.

* Calcium values expressed in mg. per 100 cc. Ratio expressed as percentage.

The exact significance of this variation in calcium diffusibility in tuberculosis is difficult to determine. If it is related in any way to the question of allergy it would appear logical to assume that the relationship should be a more constant one, since in all the patients included in this series the disease was of the "adult" or "second infection" type. It appears, however, that an increased ratio of diffusible to nondiffusible calcium is associated with the exudative type of tuberculous process with manifest clinical activity; conversely, a subnormal diffusibility ratio is associated with a predominantly productive or fibrotic lesion of low-grade activity. This finding is of interest in view of the observation by Petersen⁹ that a fibrotic tuberculous lesion is accompanied by a diminished permeability of skin capillaries as determined by the blister test, and by an increased calcium-potassium ratio in the tissues; the reverse is the case in the exudative type of lesion.

In tuberculosis, as in bronchial asthma and allied disorders, there appears to be a definite relationship between calcium diffusibility and cell permeability. Which is the primary and which the secondary factor, or whether both are secondary to an allergic state cannot be determined by the method employed in the present study. However, from the findings of Brown and Ramsdell,³⁰ referred to above, it seems that the increase in diffusible calcium in anaphylactic shock is not dependent upon increased cell permeability, since the determinations were made by the artificial membrane method.

Conclusions. Previously reported investigations of calcium balance in allergic or atopic disorders and in pulmonary tuberculosis have concerned themselves with the determination of total serum calcium and of calcium intake and output. These studies have, in the great majority of instances, revealed no deviation from the normal and have led to the belief that no demonstrable disturbance of calcium metabolism exists in these conditions. Since the work of Rona and Takahashi,³¹ establishing the partition of serum calcium into diffusible and nondiffusible fractions, considerable evidence has accumulated to indicate that the physiologic activity of calcium is dependent upon the various forms in which it exists. A disturbance of the ratio between the diffusible and nondiffusible fractions may occur, with distinct physiologic effects, without any alteration in the level of total serum calcium.

The present study appears to indicate that in bronchial asthma and allied disorders there is a definite and quite constant disturbance of calcium balance in the form of an increase in the ratio of diffusible to nondiffusible calcium. It is conceivable that this observation is related in some way to the increased capillary and cellular permeability which is believed to exist in these conditions.

In chronic pulmonary tuberculosis there is considerable variation in the diffusibility of calcium. It seems that an increased diffusibility ratio is associated with an exudative type of lesion with a high degree of clinical activity, while a decreased diffusibility ratio is associated with a productive process, relatively benign clinically. Whether or not these findings bear any relation to the problem of allergy in tuberculosis cannot be stated definitely but the implication is obvious.

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AURICULAR FIBRILLATION IN PATIENTS WITH GOITER.

I. VALUE OF QUINIDIN BASED ON THE STUDY OF 114 CASES.

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AURICULAR fibrillation is the most frequent abnormal rhythm of the heart in goiter patients. Its treatment, therefore, is one of the problems in preoperative and postoperative management. Thyroidectomy alone will often bring about regular heart action,^{1,2,3,4,5} although this may not take place for months or even years following complete subsidence of thyroid toxicity. (Cases 42, 43, 44, 45 and 46.) With the object of attempting to restore all such cases to normal rhythm before discharge from the hospital, this work was begun.

It is well known that auricular fibrillation is prone to recur in nonthyroid cases after successful treatment with quinidin. Levine and Wilmaers⁶ found that only 4 of a group of 13 successfully treated with quinidin maintained normal rhythm more than a month afterward, and none after nine months. They conclude that quinidin should not be used in those patients who previously have had congestive heart failure. Sidel and Dorwart⁷ are more optimistic in their report of failure cases. They used, however, much larger doses than is customary. Phillips and Anderson¹⁰ report 59 cases of continuous auricular fibrillation in goiter patients, 52 per cent of which were found to have normal rhythm three to six months after thyroidectomy. Quinidin was used in some of these cases. Hamilton³ estimated that 30 per cent returned to normal rhythm after thyroidectomy.

This report deals with 59 cases of postoperative paroxysmal auricular fibrillation and 55 cases of established auricular fibrillation treated in the Lahey Clinic. All of the latter were at one time or another associated with hyperthyroidism, while a few of the former followed operation for nontoxic goiters. Eighteen patients of the established group had had congestive heart failure on admission to the hospital. The diagnosis was made chiefly by auscultation in the paroxysmal type, while electrocardiographic tracings were done in practically all of the established group. Only those patients who showed auricular fibrillation on admission to the hospital and continued to have it until a day or so before operation (not less than seven days in any instance) were classed as having established fibrillation. While this report does not represent a truly consecutive study of all patients operated upon in the Clinic during this

period of observation, it approaches this ideal insofar as the author was able personally to examine and treat them.

Paroxysmal Auricular Fibrillation. In most instances this type is seen following operation. It occurs frequently following removal of nontoxic goiters, but more often after partial or subtotal thyroidectomy in patients with primary hyperthyroidism. It is frequently disturbing to the patient, but rarely does it produce any alarming systemic reaction. Its appearance, therefore, cannot be considered as a cardiac emergency. Treatment, in most instances, is indicated only for the comfort of the patient.

We had frequently used digitalis in 12- to 18-grain doses to slow this type of irregularity. Often auricular fibrillation ceased following its administration. When this study was begun, we felt it desirable to observe a controlled group to determine if digitalis were effective in stopping paroxysms. Some, therefore, were given quinidin, others digitalis, while many received neither drug. Of 59 cases of postoperative auricular fibrillation (Table I) associated with thyroid disease, 15 were given digitalis as soon as possible within twenty-four hours after the onset. In 10 of this group, auricular fibrillation ceased within twenty-four hours after the drug had been administered, while 2 continued to have this irregularity from twenty-four to forty-eight hours. One of these was stopped with quinidin and the other stopped without further medication. Three more persisted after seventy-two hours and were then successfully stopped with quinidin. Another group of 29 patients received no cardiac medication at the onset of their paroxysms. All but 7 of these stopped spontaneously within seventy-two hours. The remaining 7 were given quinidin with success. Another group of 13 received quinidin as soon as possible after the onset and stopped during the time of quinidin administration. In view of the fact that the total time during which quinidin was given was usually less than twelve hours and that all cases in this group who received quinidin ceased to have fibrillation within this time, it becomes fairly conclusive that quinidin was effective. Furthermore, a few of the digitalis group persisted after digitalizing doses of digitalis. Since these were then stopped during quinidin administration and in view of the large number that stopped spontaneously this analysis contains no evidence to show that digitalis has any action in stopping paroxysmal fibrillation. Consequently, we have discontinued the use of digitalis in this group and use quinidin only if the irregularity is distressing to the patient or if it persists after two or three days.

Established Auricular Fibrillation. Approximately 10 per cent of patients with hyperthyroidism show this abnormality. Over 90 per cent of those patients who have frank congestive heart failure associated with hyperthyroidism have this irregularity and, conversely, from 30 to 40 per cent of those having auricular fibrillation

have a history or show various degrees of this type of heart failure. Thus, from a therapeutic point of view, this group requires more consideration than the group just discussed. The possibility of embolism is to be considered in selecting these patients for quinidin therapy.

During this period of observation (June, 1927 to September, 1928), we have seen 4 cases of embolism in thyroid patients. It is well to point out that 2 of these (Cases 11 and 17) had mitral stenosis with large multiple adenomatous goiters with questionable toxicity. Quinidin was tried in the first instance without success following operation. One month later while taking digitalis the patient developed a hemiplegia at home, almost certainly from an embolus. In the second case, operation was performed without incident. One week later the patient was digitalized, the apex rate came down to sixty and multiple emboli were dislodged. Such accidents following digitalization are not infrequent in nonthyroid cases. We have never seen it in the auricular fibrillation associated with well-marked hyperthyroidism and we feel that the over-activity of the heart from thyroid toxicity tends to prevent the formation of the auricular thrombi.

The other 2 cases showing emboli were very similar (Cases 13 and 14). Both had long been known by their families and physicians to have goiters. Examination revealed symmetrical enlargement of the thyroid. Thyroid toxicity was of the mild type, but from their history it had been of a severe grade previously. Both came to us with embolic manifestations and were not operated upon. One died of thrombosis of the femoral artery and infarcts of the lung. At autopsy, there were thrombi in both auricles. The valves were normal. The other case, showing a residual hemiplegia on admission, was sent home and died suddenly one month later. On clinical examination, the heart showed no evidence of valvular disease, although there was considerable enlargement. There was also marked arteriosclerosis and a deficient renal function.

We feel these last 2 cases illustrate what may happen to a long-standing case of hyperthyroidism without operation and restoration to normal rhythm, and furthermore establish another group in which one should be cautious regarding quinidin until the relationship of quinidin to embolism is established.

Selection of Cases. We exclude from quinidin therapy any patient who has:

1. A history or clinical evidence of embolism.
2. Marked mitral stenosis with fibrillation of unknown duration.
3. Mitral stenosis with congestive heart failure.
4. Congestive heart failure associated with large feebly pulsating heart as determined by fluoroscopy.
5. Long-standing fibrillation in hyperthyroid patients in which the hyperthyroidism is of mild degree.

TABLE I.—SUMMARY OF RESULTS IN 57 CASES POSTOPERATIVE PAROXYSMAL AURICULAR FIBRILLATION.

	Untreated	Treated with digitalis.*	Treated with quinidin.†
Management during first twenty-four hours	29	15	13
Stopped during first twenty-four hours	19	10	13
Stopped during twenty-four to forty-eight hours	1	2‡	1
Stopped during forty-eight to seventy-two hours	2	1	
Persisting after seventy-two hours	7§	2§	9
Persisting after quinidin	0	0	0

* Dose digitalis varied from 10 to 29 grains.

† Average dose quinidin, 19.5 grains (3 to 39 grs.).

‡ One of these cases treated with quinidin.

§ All these treated with quinidin.

Of 55 cases of established auricular fibrillation, 7 stopped spontaneously (Table II), 8 were not given quinidin (Table III), and in 5 other cases quinidin was not successful (Table IV). Thirty-four cases were successfully treated, 4 of which recurred (Table V). Of the 34 cases successfully treated, 30 were first given treatment after operation (Table VI), while 4 of these had been given quinidin successfully before thyroidectomy, 2 of which recurred after the operation and were then again successfully restored to normal rhythm (Cases 29 and 63). Six patients received their treatment in periods of four months to four years after operation (Cases 42, 43, 44, 45, 46 and 52).

Unsuccessful Cases. The onset of toxic symptoms from administration of quinidin, which for the most part consisted of nausea, fullness of the head, or diarrhea, took place about the same time as the return to normal rhythm. Variable amounts of the drug produced toxic symptoms in those cases which were unsuccessfully treated. Often smaller doses produced toxic symptoms in those who were successfully treated than in those who were not. It does not appear, therefore, that intolerance for the drug can be the cause of failure. Coincident heart disease played the biggest factor as the cause of failure, Case 18 being the only unsuccessful case which we felt was free from cardiovascular disease. When first seen, the patient showed recurrent hyperthyroidism, which was controlled with iodine for six months, after which the iodine effect became less and less apparent and the patient began to lose weight and become clinically more toxic as her basal metabolic rate increased. Quinidin was used without effect during the remission, and again after removal of the thyroid remnant, although given to the point of tolerance. At this writing, nine months after operation, the pulse is still irregular, although the patient is free from toxic symptoms. This patient, as well as all the others in the unsuccessful group, had been digitalized before quinidin administration.

TABLE II.—ESTABLISHED AURICULAR FIBRILLATION STOPPED SPONTANEOUSLY.

Case No.	Diagnosis.	Surgery.	Conges- tive heart failure on ad- mission.	Digital- ized 1½ grains per 10 lbs. of body weight.	Time of cessation.
1	Primary hyperthyroidism	+	○	○	Thirty-six hours post-operative.
2	Adenomatous goiter hyperthyroidism	+	○	○	? Twenty-four hours postoperative.
3	Primary hyperthyroidism	+	○	○	Two days before operation.
4	Primary hyperthyroidism	+	+	○	Two hours postoperative.
5	Primary hyperthyroidism	+	○	+	After rest iodine before operation.
6	Primary hyperthyroidism	+	+	○	After first-stage operation while at home.
7	Primary hyperthyroidism	+	○	○	One hour after operation.

TABLE III.—CASES WHERE QUINIDIN WAS NOT GIVEN.

Case No.	Diagnosis.	Surgery.	Conges- tive heart failure on ad- mission.	Digital- ized 1½ grains per 10 lbs. body weight.	Reason quinidin not given and subsequent course.
8	Adenomatous goiter; hyperthyroidism; hypertension; luetic aortitis	+	+	+	Slow pulse before digitalis and Lugol's, long duration marked congestion; dying one year later.
9	Primary hyperthyroidism; arteriosclerosis; diabetes; hypertension 230/110	+	○	+	Long duration; slow pulse; might have tried later; died six months later.
10	Primary hyperthyroidism; arteriosclerotic heart	+	+	+	Slow large heart, feeble pulsations; long duration; feared embolus.
11	Mitral stenosis; large non-toxic; goiter	+	○	+	Mitral stenosis; developed emboli following digitalization after operation seven days; hemiplegia—one year.
12	Primary hyperthyroidism	○	○	+	Died; broncho-pneumonia; no operation.
13	Arteriosclerosis; primary hyperthyroidism (long standing)	○	○	○	Multiple emboli; died, pneumonia; no operation.
14	M. C. A. goiter; arteriosclerosis; chronic nephritis	○	○	○	Hemiplegia; died one month later; no operation.

TABLE IV.—UNSUCCESSFUL CASES.

Case No.	Diagnosis.	Surgery.	Congestive failure on admission.	Digitalis given $\frac{1}{4}$ gr. per 10 lbs. body weight.	Time of quinidin administration, days.	Dose of quinidin, grains.	Follow-up time.	Reaction.
15	Primary hyperthyroidism; rheumatic heart	+	+	+	6 P. O.*	12	Auricular fibrillation one year later	O
16	Primary hyperthyroidism; arteriosclerotic heart, colitis	+	+	+	First stage, 16 P. O. Second stage, 7 P. O. 7 P. O.	9 18 21	Auricular fibrillation one year later	Severe diarrhea. Severe diarrhea.
17	Mitral stenosis; adenomatous goiter	+	O	+	2 mos. A. O.†	21	Embolus one month later on digitalis	Nausea. Fullness of head, nausea.
18	Recurrent hyperthyroidism; irregular pulse since first operation elsewhere four years before	+	O	..	4 P. O. 5 P. O. 6 P. O.	18 21 36	Nine months Auricular fibrillation Nontoxic	O Nausea. Nausea. Nausea.
19	Primary hyperthyroidism; hypertension 210/110	+	O	+	3 mos. P. O. 6 P. O.	27 9	Irregular six weeks	Nausea. Nausea.

* After operation.

† Before operation.

TABLE V.—RECURRENCES.

Case No.	Diagnosis.	Surgery.	Congestive failure on admission.	Digitalis given $1\frac{1}{2}$ gr. per 10 lbs. body weight.	Time of quinidin administration, days.	Dose of quinidin grains.	Result and follow-up time.	Reaction.
20	Primary hyperthyroidism	+	○	+	First stage, 7 P. O. Second stage, 6 P. O. 7 P. O.	21	Regular recurred after second operation Irregular; ? regular three months Regular six months, recurred on taking too much thyroxin Regular six months, thyroxin reduced Regular	Slight fullness of head. Nausea. Slight nausea.
21	Primary hyperthyroidism; arteriosclerotic heart disease; ? rheumatic	+	+	+	9 mos.	27	Regular six months, thyroxin reduced Regular	None.
22	Adenomatous goiter Hypertension	+	○	○	1 A. O. 2 A. O. 3 A. O. 4 A. O. 1 P. O. 2 P. O.	39 39 39 39 39 39	Recurred when seen six months	Syncope.
23	Primary hyperthyroidism Hypertension, 200/130	+	+	+	4 P. O.	21 3 t.i.d. 1 mo.	Irregular Regular for three months then recurred	

TABLE VI.—CASES SUCCESSFULLY TREATED.

Case No.	Diagnosis.	Surgery.	Con- gestive failure on ad- mission.	Digitals given 1½ gr. per 10 lbs. body weight.	Time of quin- idin administra- tion, days.	Dose of quin- idin, grains.	Result.	Reaction.	Follow-up time in months, regular.
24	Primary hyperthyroidism	+	++	++	6 P. O.*	30	Regular	○	15
25	Primary hyperthyroidism	2 stages	++	++	First stage 1½ P. O. Second stage 2½ P. O.	0 6 21 6	Irregular Regular, recurred Regular	○ ○ ○ ○	12 12 12 12
26	Primary hyperthyroidism	+	○	○	Daily dose one month 7 A. O.†	26 15	Regular, recurred	Nausea	12
27	Primary hyperthyroidism	++	○	○	4 P. O.	9 t. i. d.	Regular	Nausea	12
28	Primary hyperthyroidism	++	○	○	6 P. O.	21	Regular, recurred	Fullness of head	12
29	Primary hyperthyroidism	+	○	○	7 P. O.	15	P. O.	○	15
30	Primary hyperthyroidism; rheumatic heart	+	○	○	3 A. O.	15	Regular	Nausea	12
31	Primary hyperthyroidism	+	○	○	3 P. O. 6 P. O.	15 27	Regular Irregular	○	11
32	Primary hyperthyroidism	2 stages	○	○	3 P. O. 4 P. O. 5 P. O. 6 P. O.	27 24 6 9	Irregular Irregular Regular	Nausea	13
33	Primary hyperthyroidism	2 stages	○	○	Daily dose to 11 P. O. 4 P. O.	24	Regular	○	12
34	Primary hyperthyroidism	+	○	○	First stage	0	Irregular	○	6
35	Adenomatous goiter; hyper- thyroidism	+	○	○	Second stage	15	Regular	○	mail report. 11
36	Adenomatous goiter; hyper- thyroidism	+	○	○	5 P. O. 10 P. O.	15 39	Regular Regular	○	6
38	Malignant adenoma; rheu- matic heart; mild hyper- thyroidism	2 stages	○	○	5 P. O.	27	Regular	○	12
39	Primary hyperthyroidism	+	○	○	5 P. O.	33	Regular	○	7
40	Primary hyperthyroidism	+	○	○	4 P. O.	33	Irregular	Fullness of head	9
41	Primary hyperthyroidism	+	○	○	First stage Second stage 7 P. O. 8 P. O.	33 27 12 15	Irregular Regular Regular Regular	Nausea ○ ○ ○	10

42	Primary hyperthyroidism, operated four years before, nontoxic	+	+	+	+	4 yrs. P. O.	21	Regular		○	10
43	Primary hyperthyroidism, operated three and a half years before, nontoxic; blood pressure, 200/100	+	+	+	+	3½ yrs. P. O.	27	Regular		○	4
44	Primary hyperthyroidism, operated two years before, nontoxic	+	+	+	+	2 yrs. P. O.	27	Regular		○	Not seen.
45	Primary hyperthyroidism, operated one year before, nontoxic	+	+	+	+	1 yr. P. O.	33	Regular	Nausea		12
46	Primary hyperthyroidism, operated one year before, nontoxic; blood pressure, 220/80	+	+	+	+	1 yr. P. O.	39	Regular	Nausea		12
47	Primary hyperthyroidism	+	+	+	+	8 P. O.	12	Regular		○	12
48	Primary hyperthyroidism; rheumatic heart	+	+	+	+	5 P. O.	12	Irregular	Nausea		12
						7 P. O.	18	Irregular		○	3
						Daily dose one month	9	Regular		
49	Primary hyperthyroidism	+	+	+	+	4 P. O.	27	Irregular	Nausea		
						3 P. O.	9	Regular, recurred		○	
						6 P. O.	27	Irregular		○	
						7 P. O.	36	Irregular		○	
						8 P. O.	24	Irregular	Nausea		
						9 P. O.	18	Irregular		○	9
						Daily dose one month	9	Regular		○	
50	Primary hyperthyroidism	+	+	+	+	7 P. O.	21	Regular		○	6
51	Adenomatous goiter; hyperthyroidism; diabetes; blood pressure, 200/120	+	+	+	+	5 P. O.	12	Regular		○	12
52	Primary hyperthyroidism	+	+	+	+	120 P. O.	24	Regular, recurred		○	12
53	Recurrent					121 P. O.	24	Regular			
						7 A. O.	18	Regular, recurred P. O.			
54	Primary hyperthyroidism	+	+	+	+	7 P. O.	18	Regular		○	12
	Primary hyperthyroidism	2 stages				First stage, 4 P. O.	21	Regular			
						Second stage	○	Irregular few hours		12
55	Primary hyperthyroidism	2 stages				First stage	33	Irregular			
						Second stage 6 P. O.	6	Regular		○	12
						Daily dose one month				

* After operation.
+ Before operation.

‡ Six weeks elapsed between first and second stage of operation.
§ Primary hyperthyroidism (exophthalmic goiter).

Successful Cases. The majority of the 31 patients in this group had their irregularity converted to normal rhythm usually on first attempt with moderate doses of the drug. Sixteen were under the influence of digitalis, while the remainder, 15 were not given the latter drug. Ten patients of this group showed congestive heart failure on admission. In all these cases there was vigorous heart action, and an increased pulse pressure. Congestive failure was easily controlled by rest, iodine, and, in all but one case, digitalis. Attempts to restore normal rhythm were not begun until the third day after operation, in most instances from the fifth to the seventh day. This gave the maximum time to await spontaneous return to normal rhythm without holding the patient unnecessarily in the hospital, and at the same time allowed for the maximum subsidence of toxicity while under our observation. The irregularity of the pulse stopped in all cases during quinidine administration, so that it seems beyond a reasonable doubt that quinidine was responsible for this.

Reactions. Nausea was produced in 21 cases, while "fullness of the head" was complained of by 3 others. Diarrhea occurred in 2 cases, while diffuse punctate skin eruption was seen in another. One patient (Case 22) had a severe reaction following larger doses than we had previously given. After such a reaction, one hesitates to prescribe as large doses as were used by Sidel and Dorwart.⁷ Although we are not certain that quinidine was the cause of the reaction, we are reporting this case in detail.

Case Report. The patient, an unmarried woman, aged sixty-two years, came to the Clinic complaining of a goiter, which she had had for twenty years. There was no definite history of thyroid toxicity, although three years before she had had a nervous breakdown and was confined to bed for a month.

The general physical examination was negative except for the following findings: There was a very slight cyanosis of the lips. Emphysematous breath sounds heard throughout the chest, with a few crackling râles at both lung bases. The blood pressure was 150 systolic and 100 diastolic, the heart was only slightly enlarged, showing no murmurs, but auricular fibrillation was present, with an apical rate of 120. There was no edema.

An adenoma about the size of an orange and almost entirely subclavicular was found in the thyroid gland. Roentgen ray plates showed the trachea deviated to the right, with moderate anteroposterior pressure on the latter structure. The basal metabolic rate was +14 per cent.

Quinidine was begun the day after admission and 156 grains were given in four days' time, with no toxic symptoms. The pulse slowed down, but did not become regular. Five days after admission the adenoma was removed without incident. Seven days after operation, the pulse still irregular, quinidine was given again, 39 grains daily for two days. On the evening of the second day, the nurse reported that the patient suddenly fell back in bed unconscious. She was slightly cyanotic, rolled her eyes, but in a few minutes returned to consciousness. The pulse was not noted.

The next day the patient received 6 grains of quinidine early in the morning. That evening when the patient was visited by one of the surgical

service, another attack occurred. The following is the note recorded at the time:

"This evening the patient was seen at 5.15. Her lips were slightly cyanotic, pulse rate was 60 and irregular and was the slowest it had been at any time. Immediately on leaving the room, the patient clutched the region of her heart with her right hand and fell backward in bed. There was an immediate loss of consciousness, but no twitchings or convulsions. There was rapidly deepening cyanosis. The pulse was not felt and auscultation failed to show any signs of the heart beat in any position. She then made convulsive efforts at breathing with apparent obstruction, but when the dressing was removed there was no evidence of the latter. The tongue was not obstructing and was pulled forward without effect. She breathed four times during the two minutes, during which there was apparently cessation of the heart beat. While oxygen and caffeine were being prepared at the end of the two minutes, the heart sounds reappeared with immediate resumption of the pulse. Her color changed shortly to a rosy red cyanosis, thence to brighter red. The mouth dropped on the left and sagged open. The pupils during the entire time were markedly dilated and the eyes glazed. With the resumption of the heart beat, there was diffuse sweating. The patient made movements of her head and after a few minutes uttered groans. Unconsciousness persisted and, on account of extreme restlessness, codein was given subcutaneously. The heart was fibrillating at a rate of 80 to 100 at this time. Consciousness returned after about an hour and a half."

The next morning the pulse was regular and electrocardiographic tracing revealed normal rhythm at a rate of 42. No further attacks occurred and the patient left the hospital soon after, feeling perfectly well. The pulse remained regular for some time, but when seen six months later, auricular fibrillation had recurred. Whether or not this was due to toxic action of the drug on the respiratory center, or whether it was due to ventricular fibrillation with cerebral anemia, is impossible to say.

Kerr and Bender⁸ report a case of syncope similar to this one in which they were able to obtain electrocardiographic tracing which showed ventricular fibrillation.

An increase in the apical rate during administration of the drug was frequently seen in other patients. This follows a slowing of the auricular rate as observed by Lewis and others.⁹ They state that if digitalis is given first, the increase in ventricular rate will be less and, therefore, less disturbing to the patient. We have not found this procedure necessary.

Method of Dosage. In most instances we have used the daily plan of dosage which we have previously described,⁵ similar to that advocated by Smith and Clark.¹¹ The order for treatment is written as follows:

R: quinidin sulphate grains three after breakfast.

If no reaction or unpleasant symptoms develop, give 6 grains with one-half glass or more of fluid every two hours until the pulse is regular, unpleasant symptoms arise, or not more than a total of 39 grains has been given.

We have found this to be satisfactory in hospital treatment and in a few cases treated at home. Because of the rapid absorption of

quinidin, we have not found it necessary to wait longer than two hours for manifestations of an idiosyncrasy to the drug. When this plan of treatment has been ineffectual, or when toxic symptoms have occurred before the heart has become regular, our next step has been to give 6 or 9 grains after each meal for several days. This may be tolerated by the patient and, if continued, may prove successful (Cases 21, 27 and 40). If no results are obtained by this procedure, the patient is then discharged with instructions to take 3 grains after each meal until his return to the Clinic. In cases where there has been some difficulty in establishing normal rhythm, we have prescribed a daily dose of 6 grains, to be continued for a month or two in order to insure permanency of the result.

Recurrences. Recurrences have been few. One patient (Case 21) entered with mild congestive failure. He showed auricular fibrillation, an old mitral lesion and arteriosclerosis. After operation the normal rhythm was restored with 9 grains of quinidin. Three months later he had developed postoperative myxedema. He was given thyroxin and when seen three months later, was again fibrillating. Clinically, as well as by the basal metabolic rate, it was evident that he was taking too much thyroxin. Quinidin was again used successfully (27 grains) and the thyroxin reduced. Six months later when seen, his pulse was regular. Another patient (Case 20) was successfully given quinidin after the first stage operation. But auricular fibrillation recurred following the second stage. Quinidin was again used, but the patient developed severe diarrhea. The patient's pulse was still irregular at the end of three months, at which time we prescribed 3 grains of quinidin to be taken after each meal. Two months later the patient reported by mail that her pulse is regular, although we cannot be sure of this until we see her again. The third case which recurred (Case 22, discussed above) did not, in our opinion, have auricular fibrillation because of hyperthyroidism. She had distinct hypertension. She was not given quinidin again because of the severe reaction described above. The fourth patient had hyperthyroidism and a coincident hypertension (Case 23). Although successfully treated at first, auricular fibrillation recurred after six months. From these experiences, we feel that recurrence of auricular fibrillation in goiter patients are usually due either to recurrence of thyroid toxicity or to coincident cardiovascular disease.

Summary. Fifty-nine cases of postoperative paroxysmal auricular fibrillation in thyroid patients have been studied to compare the relative efficacy of digitalis and quinidin. While digitalis will slow the pulse, we do not believe that it exerts a favorable action on the stopping of the paroxysms. Quinidin, in our hands, has proved successful in all cases of this type. Fifty-three cases of established auricular fibrillation, associated with goiter, have been presented

showing the clinical types met with, the selection of cases with quinidin and the results of those treated. In selected cases, quinidin has been permanently successful in 88 per cent of those treated with the drug. Iodin and thyroidectomy caused cessation in 15 per cent of all operated cases during the period of hospital observation. Iodin, thyroidectomy and quinidin resulted in a permanent return to normal rhythm in 76 per cent of all operable cases, at least for the time over which we have observed them. In hyperthyroidism uncomplicated by cardiovascular disease, return to normal rhythm may be anticipated in practically 100 per cent of cases.

Conclusions. 1. Quinidin is the most effective drug in the treatment of postoperative paroxysmal auricular fibrillation.

2. Quinidin is the ideal drug for restoration of normal rhythm from established auricular fibrillation in selected cases of hyperthyroidism.

3. The plan of two hourly dosage is practical, no more dangerous in our hands than other methods, and is valuable as a time saver.

NOTE.—Since the paper was written, we have been successful in having 48 patients return for examination who had had established auricular fibrillation at the time of their operation from two to seven years before. Quinidin had not been given to this group. Twenty-five (52 per cent) of these patients showed normal rhythm, the same as the per cent reported by Phillips and Anderson.

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THE ABSORPTION OF GLUCOSE PER RECTUM.

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THE administration of glucose per rectum is a widely used procedure. Yet few generally accepted modes of therapy have had so little control study. Observations on blood sugar changes following the injection of rectal glucose have been made by Varela and Rubino,^{1,2} Tallerman,³ Levi⁴ and others. For the most part, results obtained strongly indicate that no marked rise in blood sugar level occurs, but on the contrary there results an actual lowering, without preliminary hyperglycemia.

Levi's⁴ work on diabetics is particularly enlightening. He finds in 8 cases of diabetes mellitus that after giving 50 to 80 gm. of dextrose rectally there occurs an average rise of only 11 mg. at one-half hour, followed by a sharp and rapid drop in blood sugar values, the level after two hours being 29 mg. below the fasting figure (209 to 180). Four of his 8 cases showed no rise during any period of the observation. These findings in diabetics are particularly significant since at the high blood sugar levels which existed, the amount of the rise did not exceed experimental limits of error of the method, and it is well known that any appreciable absorption of sugar will be reflected in the diabetic.

This drop in blood sugar occurring in the normal is in all probability a manifestation of postalimentary hypoglycemia, despite the fact that no preliminary rise has taken place. Following the introduction of even very small quantities of glucose into the blood stream, whether directly or by absorption from the intestinal tract, a change takes place whereby metabolism of glucose occurs more rapidly than under fasting conditions and hypoglycemia results. As Jordan⁵ has proven, this change is a hyperinsulinism due to stimulation of the islands of Langerhans by the hormone action of the absorbed glucose.

The drop in blood sugar after administering glucose rectally is not, therefore, dependent upon complete absorption having taken place or a preliminary hyperglycemia, but can occur after trivial amounts of glucose have been absorbed, and with the bulk of the glucose enema remaining in the lumen of the bowel, since we know from Jordan's⁵ experiments, that quantities of absorbed glucose too small to be reflected in the urinary output of sugar still have the power of stimulating insulin production. Other evidence tending to indicate that postalimentary hypoglycemia is not dependent upon

complete absorption, is at hand. Cajori, Crouter and Pemberton⁶ quote the work of Foster, and DuVigneaud and Karr⁷ support the observations of Johansson, MacLean, DeWesselow and others, who have shown that during the hypoglycemia following a preliminary rise, second doses of glucose result in no further rise of the blood sugar level. Jordan⁸ points out the work of Thalheimer, Raine, Perry and Buttles, who injected glucose into the veins of dogs continuously over a period of two hours and observed that while a rise in blood sugar took place during the first hour, the blood sugar level actually fell during the second hour, and when the injection was stopped, an extremely rapid drop took place, resulting in severe symptoms like those of insulin shock. It is conceivable therefore, that the hypoglycemia which is believed to follow rectal administration of sugar, can take place, even though a large part of the glucose introduced still remains within the lumen of the rectum.

It has already been pointed out that Levi⁴ found no significant rise in blood sugar levels in diabetics given glucose by rectum. Luthje (quoted by Carpenter⁵) conducted further experiments on diabetics and was able to demonstrate that while small doses of glucose by mouth resulted in increased urinary sugar output, no such rise followed the administration of 100 gm. by rectum, but on the contrary, the rate of sugar elimination actually fell. In the light of these experiments, it is not conceivable that any considerable absorption of sugar had taken place.

Carpenter,⁵ however, has demonstrated that when patients are given glucose by rectum, there is a distinct shift toward a carbohydrate metabolism level, indicating that under these conditions a higher proportion of sugar is burned than in the normal fasting individual. This phenomenon does not necessarily mean that any great quantity of glucose has been absorbed. Under the conditions of his experiment we have no means of knowing whether the shift represents utilization of sugar equivalent in amount to that absorbed, or whether sugars previously stored in the body have been burned in excess, as the result of stimulation to carbohydrate metabolism resulting from the hormone action of a relatively small amount absorbed. In either case, changes in respiratory quotient would be the same. If the latter be true and sugar is burned in excess of that actually absorbed, we should find some indication of a depletion of the sugars previously stored, and such evidence is, in fact, suggested in the form of the lowered blood sugar level reported found after rectal administration of solutions of glucose. We must, therefore, not be too hasty to accept the change in respiratory quotient as indicating the absorption of large amounts of sugar; for in all probability the increased carbohydrate metabolism takes place to a greater degree than can be accounted for by the utilization of absorbed glucose *per se*. Only by this explanation can we account for the lowering of the blood sugar occurring without a preliminary

rise, for it is apparent that stored sugars are being burned more rapidly than they can be replaced by the relatively slow rectal absorption.

If the drop in blood sugar is greater than occurs from the normal utilization of sugar during a fasting period, and no preliminary rise has taken place, it is obvious that glucose is being burned more rapidly than it is absorbed, which is important in view of the fact that glucose is usually given per rectum only in those cases where sugar depletion is already present or likely to occur. The status of sugar deficiency would then be aggravated rather than improved by the instillation of sugar *via* the rectal route.

There is no positive evidence in the literature to indicate the ultimate fate of all the glucose introduced in this fashion. A large part of it can be recovered in the stools many hours after the instillation. Carpenter⁵ points out the following experiments: Zémisch, in 1905, recovered 32 per cent of 150 gm., injected over a two-day period. Heile found a return in the stool of 94 per cent and in a second experiment 75 per cent after one hour. Varela and Rubino¹ recovered 60 per cent but do not give the details of recovery. Many other similar results are reported.

If glucose does remain in the bowel for long periods and in large quantities, we must consider what part is lost by way of fermentation as the result of bacterial action of the intestinal flora. To determine this, Bingel (quoted by Carpenter⁵) fermented glucose with feces and found a disappearance of 34 per cent and 28 per cent of the planted glucose after five hours of incubation.

No experiments have been reported to indicate that the drop in blood sugar level which has been found following rectal administration of glucose exceeds the drop during a similar fasting period without the introduction of sugar, nor have comparisons been made to demonstrate the blood sugar reactions in the same patient when glucose is given by mouth and by rectum under otherwise similar conditions. The scope of this paper is to indicate what changes in blood sugar take place when sugar is introduced per rectum, to compare these changes with those following the introduction of equal quantities of glucose by mouth, and to point out how these variations differ from blood sugar level curves during a similar fasting period when no glucose is introduced.

Determinations of the sugar residue of the stools of patients whose blood sugar curves are reported will be given in order to demonstrate the actual quantities of glucose remaining in the bowel several hours after its administration, and experiments will be described to point out the rate of destruction of glucose from fermentation due to the action of the bacterial flora of the intestinal tract.

Method. Bearing in mind the observations of Rubino and Varela² and the conclusion of Carpenter⁵ that "the higher the

concentration of the solution or the higher the weight of glucose actually introduced, the greater is the absorption," we used in each case, a 33 per cent solution of C.P. dextrose, made up with 80 gm. of the sugar in 240 cc. of plain tap water, at body temperature.

Patients were males in middle life without colonic or metabolic diseases, for the most part being treated for minor injuries. Following the ordinary hospital meal at 5.30 P.M. the previous evening, subjects were starved for fourteen hours. The following morning a cleansing soap-suds enema was given. An hour later a fasting blood sugar was taken, all blood specimens being preserved in sodium fluoride, and then 240 cc. of the 33 per cent dextrose solution introduced with an ordinary soft rubber rectal tube passed into the ampulla. Instillation was over a ten-minute period. Patients were kept entirely at bed rest, and the glucose enema retained throughout the length of the experiment (four hours). Blood specimens were taken just before the glucose was introduced and forty-five minutes, one and a half hours, three hours, and four hours afterward, and analyzed immediately after the taking of the last specimen.

The following morning upon the same patients after a similar fasting period, a fasting blood sugar was taken, 80 gm. of C.P. dextrose in about 350 cc. of water flavored with orange and lemon were given by mouth, and blood sugars taken after one-half hour, one hour and two hours, in order to obtain a basis of comparison for the changes occurring after rectal administration.

As a control, two normal patients were treated as the others who had been given the glucose by rectum, except that a 5 per cent salt solution was substituted for the 33 per cent glucose, and blood taken at intervals over a four-hour period, and analyzed for sugar.

All of the patients given the rectal instillations suffered some discomfort, usually moderate, but only one was forced to pass the enema before the end of the experiment.

Blood sugar analyses were by the Folin-Wu method and performed through the courtesy of Dr. A. H. Zeiler by the laboratory of Drs. Brem, Zeiler, Hammack and Maner, Los Angeles.

The changes in blood sugar occurring in a normal individual between the fourteenth and eighteenth hours of a fast period, are indicated by those of our patients who received saline by rectum, and the results are in keeping with those reported by Varela and Rubino² who, however, present no actual figures. Our results are tabulated in Table I. The average fasting level after fourteen hours is 90 mg. per 100 cc. with a very slow, steady, gradual decline to 86 at the end of the eighteenth hour, a drop of only 4 mg. during this four-hour period.

Results obtained after the rectal injection of 80 gm. of C.P. glucose in 240 cc. of water as described above, are given in Table II. They are presented together with the blood sugar readings of these same patients after an equal quantity of glucose had been given by mouth.

TABLE I.—CHANGES IN BLOOD SUGAR IN MILLIGRAMS OCCURRING BETWEEN THE FOURTEENTH AND EIGHTEENTH HOUR OF A FASTING PERIOD.

	Fasting.	$\frac{1}{2}$ hr.	1½ hrs.	3 hrs.	4 hrs.
Patient 1 . . .	84	80.0	85.0	84	80
Patient 2 . . .	96	95.0	94.0	90	92
Average . . .	90	87.5	89.5	87	86

Two hundred and fifty cubic centimeters of 5 per cent saline solution introduced after fasting sugar was taken.

TABLE II.—CHANGES IN BLOOD SUGAR IN MILLIGRAMS FOLLOWING ADMINISTRATION OF 80 GM. OF GLUCOSE.

	Route.	Fast-ing.	$\frac{1}{2}$ hr.	$\frac{1}{2}$ hr.	1 hr.	$\frac{1}{2}$ hrs.	2 hrs.	3 hrs.	4 hrs.	Maximum change.
Patient 1 {	M	103	166	..	167	..	142	+64
	R	122	..	118	..	111	..	108	103	-19
Patient 2 {	M	101	...	101	...	103	Enema expelled			
	R	101	...	101	...	103				
Patient 3 {	M	108	Glucose	by mouth refused				109	93	+18
	R	108	..	126	..	105	..	109	93	+18
Patient 4 {	M	105	216	..	222	..	162	+117
	R	100	..	88	..	87	..	86	90	-14
Patient 5 {	M	123	150	..	162	..	138	+39
	R	119	..	101	..	99	..	89	100	-30
Patient 6 {	M	111	140	..	184	..	152	+73
	R	104	..	91	..	93	..	86	85	19
Patient 7 {	M	115	158	..	148	..	144	+43
	R	86	..	95	..	92	..	92	87	+9
Average {	M	111	166	..	176	..	146	+65
	R	106	..	103	..	99	..	94	92	-14

M—80 grams of sugar in 350 cc. of water, by mouth.

R—80 grams of sugar in 250 cc. of water, by rectum.

The sugar curves after oral administration are reasonably typical of the accepted normal. In those cases (Patients 4 and 6) in which the blood sugar level exceeded 180 mg. the urine was positive for sugar by Benedict's test, at the height of the curve. All other urine specimens were negative for sugar.

The curves following rectal administration require more careful analysis. In only 2 of the 7 patients was there any rise. Patients 3, an excitable Mexican, presented an initial rise of 18 mg. which dropped to fasting level at the end of one and a half hours. Patient 7 presented an initial rise of 8 mg. (as compared with an initial

rise of 43 mg. when glucose was given by mouth) and then a steady decline to fasting figures. The remaining subjects each showed an actual drop in blood sugar readings, the greatest being a decrease of 30 mg. (Patient 5), at the end of three hours.

Throughout the length of the experiment, except for the two exceptions already noted, the average drop in blood sugar was constant and steady without rises at any time. The average curve of our series of cases, when plotted, is practically a straight line, gradually dropping off from the high fasting level to the lower figure at the end of the experiment. This demonstrates that the drop in blood sugar values takes place in a steady progression from one hour to the next, the average level at the end of four hours being 14 mg. below fasting, as compared with a drop of only 4 mg. when no glucose was introduced into the body. In other words, the drop in blood sugar level is three and one-half times as great when sugar in these quantities is instilled into the rectum, than when no sugar is introduced.

After the final blood sugar had been taken, the first stool passed was recovered without rectal washings of any kind, and analyzed for its sugar content. Analyses were by the Folin-Wu method. No difficulty in technique was encountered for the stools were all watery and relatively clear.* One patient retained the sugar enema for seven hours. In this latter case, specimens were examined after seven, ten and thirteen hours, the first analysis yielding 26.2 gm., the second 1.9 gm., and the third after thirteen hours, less than 1 gm. of the 80 gm. introduced. Results are indicated in Table III.

The two latter figures do not appear in the table.

TABLE III.—RECOVERY OF GLUCOSE FROM STOOL: 80 GM. INTRODUCED.

Patient.	1.	2.	3.	4.	5.	6.	Average.
Hours after introduction	7.0	4.0	4	4.0	4.0	3.0	4.3
Grams recovered	21.0	10.0	16	33.6	10.0	25.0	19.2
Percentage recovered	26.2	12.5	20	42.0	12.5	31.2	24.0

From these studies it is apparent that four hours after the injection of 80 gm. of glucose per rectum, an average of 24 per cent of this amount could not conceivably have been absorbed for it still remained in the lumen of the rectum and was returned in the stool. In one case 26.2 per cent was recovered after seven hours.

Fermentation experiments to determine the rapidity with which glucose is destroyed by the fermentative action of the intestinal flora were carried out. Glucose, feces and water were combined so that the quantities of glucose were 5 per cent and 3 per cent respectively, the quantity of stool constituting roughly 40 to 50

* To determine the accuracy of our analysis of the sugar content of stools, sugar in known amount was added to a stool, and the mass analyzed for sugar. (Dr. A. H. Zeiler.) In no case did an error of more than 0.3 per cent occur.

per cent, the mass totaling about 100 gm. At the end of seven hours of incubation, analysis by the picramic method revealed that only 0.5 per cent of glucose in the first case and 0.4 per cent in the second experiment remained. Other specimens were taken at ten and thirteen hours and resulted in a further drop of about 0.1 per cent at these times. (Brem, Zeiler, Hammack and Maner Laboratories.) The masses were filled with bubbles of gas and much fermentation had taken place. The figures obtained demonstrate that approximately 90 per cent of the planted glucose had been destroyed after seven hours.

This observation, coupled with the fact that 25 per cent or more of injected glucose remains in the bowel for a period comparable to the elapsed time before the first analyses of the fermentation experiments were made, strongly indicates that much of the sugar we have introduced remains in the intestinal tract and undergoes fermentation, rather than becoming available to the body for metabolic purposes.

Discussion. There can be no question but that a small part of a quantity of glucose introduced per rectum is absorbed and acts as a stimulant to insulin production, destroying larger amounts of sugar previously stored. This assumption is necessary to account for the increase in sugar metabolism which takes place as evidenced by the rise in respiratory quotient and the lowering of blood sugar. That the amount absorbed is not great can be deduced from the observation that no rise in blood sugar and no increase in sugar elimination takes place even in the sugar sensitive diabetic. By comparing our figures with those in the literature it is obvious that the concentration and period of time devoted to the instillation are not factors in the ultimate result nor can it be argued that nearly complete absorption does take place, but too slowly to be reflected by a rise in blood sugar for Staube (quoted by Carpenter⁵) has shown that repeated feedings by mouth of very small quantities of glucose, results in an increase of the sugar content of the blood.

From the evidence at hand, we are not free to draw definite conclusions concerning the therapeutic value of glucose by rectum; but this must be left for observations upon the reactions of patients having definite need for glucose.

When we consider that the ordinary Murphy drip or small repeated enemata given in the usual fashion introduces over a twenty-four-hour period only 75 to 150 gm., equivalent to 300 to 600 calories, and that much of this is lost by nonabsorption and passed out in subsequent stools, and that fermentation destroys another very appreciable quantity, we must realize, even without looking further into the problem, that the rectal administration of sugar is not a satisfactory therapeutic procedure in that it fails in its intended

purpose of making available to the organism an appreciable quantity of utilizable sugar.

Summary. Seven fasting patients were given 80 gm. of glucose by rectum and on the next day an equal quantity by mouth. Blood was analyzed at intervals for sugar content and it was found that when glucose was given by mouth an average maximum rise of 65 mg. per 100 cc. of blood took place. Following rectal administration no such rise resulted, but on the contrary the average blood sugar level fell after four hours, from 106 to 92, a drop of 14 mg. This compared with a drop of only 4 mg., when, under otherwise similar conditions, saline was substituted for the glucose per rectum. These findings were interpreted as indicating that sufficient absorption had taken place to stimulate insulin production, resulting in an increased metabolism of previously stored sugar, but that the absorption from the rectum had not been sufficiently rapid to replace the body sugars so destroyed.

We have pointed out that the increase in respiratory quotient may be due not to the absorption and utilization of an equivalent amount of sugar absorbed by the rectum but rather to the metabolism of sugars previously stored, the increased rate of destruction being due to a hyperinsulinism, which results as Jordan⁸ has proven when small quantities of glucose are introduced into the body.

The stools of patients given sugar by rectum were analyzed for sugar content, and four hours after introduction as much as 42 per cent (Patient 5) of the introduced glucose was recovered in the stool. The average recovery after four hours was 24 per cent, and in one case 26 per cent was recovered in a single stool seven hours after the introduction of the glucose.

To determine how much fermentation might be expected to take place in the rectum, glucose and feces were combined and incubated for thirteen hours. Specimens examined at seven hours showed that destruction of nearly 90 per cent of the glucose had taken place.

Conclusions. From these observations it can be concluded, that:

1. Following the introduction of glucose into the rectum blood sugar levels fall without a significant preliminary rise.

2. This fall is greater than that occurring during a corresponding fasting period when saline is introduced instead of glucose.

3. The bacterial content of the lower bowel rapidly ferments glucose.

4. Absorption of glucose by the rectum is sufficiently slow to permit fermentation to take place, 25 per cent of the introduced glucose having been recovered in stools four hours after a glucose enema.

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**PRESSURE AS A FACTOR IN THE DEVELOPMENT OF NEURITIS
OF THE ULNAR AND COMMON PERONEAL NERVES
IN BEDRIDDEN PATIENTS.***

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NEURITIS not uncommonly develops in patients who are on the highway to recovery from prolonged and severe illnesses. It is often alarming to the patient, and because of its persistence soon proves to be disturbing to the physician. The surprising frequency with which only the ulnar or common peroneal nerves may be involved stimulates one's interest. Neuritis usually has a toxic or infectious basis, and the toxic or infectious agents often possess canny specificity in their choice of nerves (for example, neuritis in the upper extremities due to lead and neuritis in the lower extremities due to arsenic). Therefore, the inviting explanation that the cause of the forms of neuritis under discussion is toxicity or infection has been the one generally accepted. Singer, who has contributed an excellent monograph on disorders of the ulnar nerve, evidently was not altogether satisfied with this explanation. He advanced the view that the highly organized segmental function subserved by the ulnar nerve may account for its ready vulnerability.

The unprotected situation of the ulnar nerve at the internal condyle and of the peroneal nerve at the neck of the fibula, and the closeness of these nerves to bony structures must be potential sources of danger. The observation of a number of cases of paralysis

of these nerves, as they developed in prostrated patients, has led me to the belief that compression is a factor of greater importance than is generally granted.

Cases Illustrative of Disturbance of the Ulnar Nerves. CASE I.—A controller, aged forty-nine years, had suprapubic pain and dysuria. Examination disclosed carcinoma of the bladder, marked cystitis and moderately high blood pressure. Suprapubic cystostomy was performed and radium was applied to the growth. For a period of two weeks, the patient suffered intense pain, which necessitated frequent administration of morphin; during this time he lost much in weight. When his general condition improved, he complained of numbness and weakness of the hands. On neurologic examination, almost complete motor paralysis and a moderate degree of sensory paralysis in the fields of both ulnar nerves was found; he related that while he had been in agony he had sunk his elbows heavily into the bedding at his sides. When he returned for reexamination three years later, there was no evidence of recurrence of the carcinoma, and the paralysis and numbness had disappeared completely.

CASE II.—A physician, aged sixty years, had difficulty in passing urine. He had become very ill and had lost 30 pounds in weight. Examination disclosed that the obstruction was due to enlargement of the prostate gland, for the relief of which suprapubic cystostomy was done. After lying in bed on his back for about two weeks, he complained of numbness, limited strictly to the distribution of the ulnar nerves. Objectively, neither weakness nor anesthesia were found.

CASE III.—A housewife, aged forty-eight years, complained of frequent and painful urination and general malaise. The diagnosis was ulcerative cystitis and pyelonephritis. The systolic blood pressure was 200 mm. and the diastolic pressure 104 mm., measured in millimeters of mercury. She had lost 24 pounds in weight. After having lain in bed on her back for a month, she complained of continuous tingling and numbness of the hands. Examination disclosed slight diminution in sensation over the distribution of both ulnar nerves. This disappeared as her general health improved.

CASE IV.—A housewife, aged twenty-nine years, and weighing 93 pounds, said that she had been "run down" all of her life. Before coming to The Mayo Clinic she had spent many months in bed, with her elbows resting on the bed and her hands crossed over her abdomen. Gradually, annoying numbness had developed over the distribution of both ulnar nerves. Examination disclosed mild hypertension, an ovarian cyst which had not produced symptoms, and a basal metabolic rate of -16 . The numbness gradually disappeared after the patient had been dislodged from her bed and had been supplied with both physical and mental support.

CASE V.—A laborer, aged sixty-three years, had suddenly lost consciousness and had fallen to the floor, where he had lain for three days. When he had recovered consciousness, he had discovered a bed sore over the sacrum, and weakness and numbness of both hands. Since the onset of his illness he had lost 40 pounds in weight. Examination disclosed bilateral ulnar palsy of moderate degree and evidences of cerebral arteriosclerosis; the latter presumably accounted for the attack of unconsciousness.

Cases Illustrative of Disturbance of the Peroneal Nerves. CASE VI.—A barber, aged forty-one years, over a period of six months had gradually slipped into a state of extreme mental dilapidation, accompanied by symp-

toms and signs of increased intracranial pressure. He had lost greatly in weight and appeared to be moribund. The muscles supplied by the peroneal nerves were moderately paralyzed and sensory tests showed slight impairment in the distributions of these nerves. The normal popliteal concavities had become so obliterated by loss of weight that the upper ends of the fibulas rested hard on the surface of the bed. After the evacuation of a large subdural hematoma, the patient made a rapid recovery from all symptoms.

CASE VII.—In a student, aged seventeen years, bilateral otitis media had developed. He had failed to recover, and during the ensuing months had become so feeble and emaciated that he had been confined to bed. Symptoms of a brain abscess appeared, but localization of it was not possible. At a second exploration, material from a huge abscess was evacuated from the right temporal lobe. He rallied quickly, and it was then discovered that complete bilateral sensory and motor paralysis of the peroneal nerves had developed. In due course of time he recovered completely.

CASE VIII.—A postal clerk, aged fifty-four years, had become very ill with symptoms of exophthalmic goiter. He had been confined to bed for several weeks and had lost 22 pounds in weight. Following thyroidectomy and while he was still in bed, there appeared marked motor and slight sensory paralysis of the left peroneal nerve. When he was last seen there was marked improvement from the paralysis.

CASE IX.—A woman bookkeeper, aged sixty-seven years, had had symptoms of gall stones. Examination disclosed, in addition, a systolic blood pressure of 180 mm. and a diastolic pressure of 90 mm., measured in millimeters of mercury. While the patient was confined to bed following operation, paralysis and numbness of moderate degree appeared in the distribution of the right common peroneal nerve and palsy of slight degree in that of the left. When the patient was last heard from she had recovered completely.

Comment. In these cases, either the ulnar or the peroneal nerves alone were involved; there was no suggestion of peripheral neuritis elsewhere. In all cases but one, the affliction was bilateral. None of these patients had used alcohol. Injury to the ulnar nerve by the edge of the operating table could be excluded in 3 cases of the first group, since an operation had not been performed and on the basis of the history, it was hardly to be considered in the remaining two. There was no evidence of luxation of the nerve, and no deformity of the elbow. Of the 4 patients in the second group, with symptoms referable to the peroneal nerves, 3 were males, resembling in sex incidence that noted in palsy from crossing the legs.⁸ A toxic infectious state is usually blamed for the production of neuritis. Infection is ubiquitous and difficult to disprove; in 2 of the 5 cases of ulnar neuritis and in 2 of the 4 cases of peroneal neuritis, infection could not be demonstrated.

Singer stated that complicating ulnar neuritis alone occurs most often with typhoid fever and during the puerperium. It has also been observed that when neuritis complicates typhoid fever, it appears during convalescence. This implies that the patient has been in bed for a long time.

Singer granted that pressure may be a factor in the development of ulnar neuritis in those cases in which the arm is thrown across the bed in such a manner that the nerve is compressed by the hard edge of the bed, or in which the arm is thrown over the head. In the latter case the mechanism is quite different; the nerves probably are pinched between the clavicle and the cervical spine or between the clavicle and the first rib and the plexus rather than the ulnar nerve alone is usually implicated. In Peel's case of ulnar palsy, the patient had slept on her face, with the arm placed under the abdomen to relieve pain. In commenting on ulnar neuritis, Seeligmüller assigned some importance to pressure as a cause. Lloyd was more emphatic; in reporting the case of a patient who had had typhoid fever and in whom, subsequently, ulnar palsy developed, he expressed the opinion that pressure, rather than a toxin, was responsible for such cases of palsy; however, he mentioned that he could not exclude injury by the attendants as a possible factor. Oppenheim stated that pressure may cause ulnar neuritis in emaciated patients who are confined to bed. My experience indicates that pressure on the hard arms of a chair may also contribute to the production of neuritis. The evidence in my cases suggests that the ulnar or peroneal nerves had been compressed between a bone and the underlying surface.

Lüderits, Stopford, and others have observed that in neuritis due to pressure, involvement of motility occurs before sensory disturbance. This was not true in the cases of ulnar palsy in which sensation and motility were involved equally or in which one was affected as often as the other. In the cases of peroneal palsy, however, motility was always more affected than sensation, except in Case VII, in which both were completely paralyzed. Disease of the blood vessels is a factor on which Lapinsky laid great stress in a discussion of the production of senile and arteriosclerotic neuritis, and it is likely that pressure also may interfere with the blood supply to the nerve.

Traction also may produce paralysis of the common peroneal nerve. This was seen in a case of spinal gliosis in which the lesion in the spinal cord had produced such an alteration in tonicity that extreme genu recurvatum had been produced; this resulted in peroneal palsy of peripheral origin. The forcible correction of ankylosis of a knee in flexion also may result in peroneal paralysis. Most of the patients that I have observed, particularly those in whom peroneal neuritis developed, had been extremely ill, and had lost greatly in weight and in muscular tonus. The popliteal recesses had become obliterated and the heads of the fibulas, unduly prominent. Evidently stretching of the ligamentous supports of the knees had taken place so that partial genu recurvatum could occur. This would add the factor of traction.

Summary. Selective paralysis of the ulnar or peroneal nerves not infrequently occurs in bedridden patients. The assumption that the causes of these forms of paralysis are infection or toxicity would seem to be true only in part. Compression of these nerves between the bone and the underlying surface and, in the patients with peroneal palsy, additional traction on the nerve and on the muscles supplied by this nerve, seem to be important but generally neglected factors. Interference with the blood supply to the nerve, and loss in weight, which deprives these nerves still further of their protective coverings, evidently contribute. Preventive measures include massage, attention to the bedding, proper support and position of the limbs, and care that the covers, when they are tucked in, do not draw the feet too tightly downward. Subsequently heat, massage, and mechanical support may be prescribed. Although recovery may be delayed for several months, it may be anticipated.

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A STUDY OF INTESTINAL TUBERCULOSIS AMONG EXSERVICE MEN.*

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TUBERCULOUS infection of the intestines may occur by direct invasion from the lumen, through infection from tuberculous lymph glands, or through the blood stream. There are two clinical forms of intestinal tuberculosis—the secondary or ulcerative type commonly seen in cases of advanced pulmonary tuberculosis, and the primary or hyperplastic type, the latter being more frequently encountered abroad than it is in this country.

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Stewart,¹ as reported by Barrington-Ward, states that 71 per cent of the hopeless cases of pulmonary tuberculosis at the Manitoba Sanatorium developed symptoms and signs of intestinal tuberculosis; of the far-advanced cases, one-third had definite signs; and of the moderately advanced cases, one-third had suspicious signs of intestinal tuberculosis. Schwatt and Steinbach found tuberculous disease of the intestines with ulceration in 65.3 per cent of 100 consecutive autopsies. Berghoff² reports that this condition is present in probably 50 per cent of all cases of far-advanced pulmonary tuberculosis.

On account of the fairly large number of cases of intestinal tuberculosis observed in the U. S. Veterans' Bureau, it was decided to make a study for the purpose of ascertaining the methods of diagnosis, the regimens used in its treatment, and the results of the various forms of treatment. Particular study was made of the effects of heliotherapy, both natural and artificial, on this condition, and an attempt was made to learn if heliotherapy resulted in reparative and healing processes of the tuberculous ulcerations of the alimentary tract, as shown by postmortem findings.

Incidence. The clinical symptomatology and signs of this disease are vague and frequently it is most difficult to recognize the condition because of the fact that pulmonary tuberculosis is accompanied by functional gastrointestinal disturbances which cannot be differentiated from those due to tuberculosis of the intestine. Consequently, if dependence is placed only on clinical symptoms and signs, a large number of cases of intestinal tuberculosis would remain undiagnosed.

Therefore, in consonance with the views of the Trudeau Sanatorium, all patients with pulmonary tuberculosis should undergo a roentgenologic examination for the purpose of ascertaining whether or not tuberculosis of the intestines coexists.

In reviewing the U. S. Veterans' Bureau postmortem protocols for 1928 it was found that 200 patients had died from pulmonary tuberculosis. Of this number, 121 (60.5 per cent) showed evidence of a coexisting intestinal tuberculosis, and 79 (39.5 per cent) had no intestinal involvement as seen at autopsy.

Period of Observation. Table I indicates the period of observation of the group of Bureau patients with intestinal tuberculosis. It is noted that the largest number were under hospitalization for various periods less than one year (69.9 per cent).

Age of Patients. M. J. Stewart³ found that more than one-third of the cases of intestinal tuberculosis, in a series of 1000 autopsies, were among patients under the age of thirty years. This observer also noted that in a series of cases with carcinoma of the intestine 84.5 per cent were over forty years of age; while in a group of cases of hyperplastic intestinal tuberculosis 80.9 per cent were under forty years of age, thus emphasizing the importance of age in differentiating between tuberculosis and carcinoma of the intestine.

The Bureau patients studied constituted a select group, by this it is meant that approximately 90 per cent of all of the exservice men fall within the ages of twenty to forty years, and 10 per cent within

TABLE I.—PERIOD OF OBSERVATION.

Age.	Number of cases.	Per cent.
Less than 3 months	229	27.0
3 to 5 "	177	20.9
6 to 11 "	187	22.0
1 to 2 years	164	19.3
2 to 3 "	56	6.6
3 to 4 "	24	2.8
4 to 5 "	7	0.8
5 to 6 "	5	0.6
Total	849	100.0

the age groups above forty years, so that the findings relative to the age distribution are not of much importance and no definite deductions can be made from the data of Table II.

TABLE II.—AGE OF PATIENTS UNDER TREATMENT FOR INTESTINAL TUBERCULOSIS.

Age.	Number of cases.	Per cent.
21 to 25 years	34	4.0
26 to 30 "	225	26.5
31 to 35 "	360	42.4
36 to 40 "	162	19.1
41 to 45 "	42	5.0
46 to 50 "	17	2.0
51 to 55 "	7	0.8
56 to 60 "	2	0.2

Distribution and Character of Tuberculous Lesions of the Lungs in Intestinal Tuberculosis. The classification of the pulmonic disease according to the schema of the American Sanatorium Association in the group of patients studied showed that 93.95 per cent were far advanced, 4.39 per cent were moderately advanced, and 1.66 per cent were minimal.

Table III indicates the distribution and the character of the tuberculous lesions of the lungs in the group of 841 cases studied.

A review of the data in the table indicates that intestinal tuberculosis is apt to coëxist in cases of pulmonary tuberculosis characterized by exudative or fibroexudative lesions with cavity formation.

Interval of Time Between Diagnosis of Pulmonary Tuberculosis and Detection of Intestinal Complication. Functional gastrointestinal symptoms are prevalent and are commonly seen in pulmonary tuberculosis. These functional digestive symptoms simulate those due to intestinal tuberculosis so that it is frequently impossible to differentiate one set of symptoms from the other. It is particularly difficult to ascertain the exact time when intestinal tuberculosis has

its inception. Erickson,⁴ in a study of 100 cases of intestinal disease complicating pulmonary tuberculosis, found that the greatest incidence was from the twelfth to the eighteenth month after the onset of the pulmonary disease.

TABLE III.—DISTRIBUTION AND CHARACTER OF TUBERCULOUS LESIONS OF THE LUNGS IN PATIENTS HAVING INTESTINAL TUBERCULOSIS.

	Exudative.		Fibrotic.		Exudative and fibrotic.		Total.	Per cent.
	With cavitation.	Without cavitation.	With cavitation.	Without cavitation.	With cavitation.	Without cavitation.		
Unilateral	1	6	5	18	14	5	49	5.8
Bilateral with less than one-third of better lung involved	14	6	14	24	55	27	140	16.6
Bilateral with more than one-third of better lung involved	244	24	25	9	321	29	652	77.6
Total cases	259	36	44	51	390	61	841*	100.0
Per cent	30.8	4.3	5.2	6.1	46.4	7.2	..	100.0

* Six cases were reported as having no pulmonary tuberculosis; 2 cases were reported as undetermined.

The data noted in Table IV constitute the opinion of Bureau physicians on the interval of time between the diagnosis of pulmonary tuberculosis and the detection of an intestinal complication.

TABLE IV.—INTERVAL OF TIME BETWEEN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS AND CLINICAL EVIDENCE OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Less than 1 month	40	4.8
1 to 6 months	70	8.3
7 to 12 "	58	6.9
1 to 2 years	141	16.7
2 to 3 "	138	16.4
3 to 4 "	92	10.9
4 to 5 "	66	7.8
5 to 6 "	50	5.9
6 to 7 "	57	6.8
7 to 8 "	50	5.9
8 to 9 "	25	3.0
9 to 10 "	29	3.4
10 to 11 "	6	0.7
11 to 12 "	5	0.6
16 "	1	0.1
Unkown	15	1.8
Total	843*	100.0

* Six cases reported as having no pulmonary tuberculosis.

Duration of Symptoms of Onset of Intestinal Tuberculosis. As was stated, the symptoms of onset of intestinal tuberculosis are as a rule vague, so that in a great many instances it is difficult to definitely recognize the condition. A study was made of the symptoms of onset of the Bureau patients having intestinal tuberculosis and the results may be seen by referring to Table V.

TABLE V.—DURATION OF SYMPTOMS OF ONSET OF INTESTINAL TUBERCULOSIS.

Age.	Number of cases.	Per cent.
Less than 1 month	114	13.4
1 to 6 months	304	35.8
7 to 12 months	129	15.2
1 to 2 years	113	13.3
2 to 3 "	56	6.6
3 to 4 "	34	4.0
4 to 5 "	15	1.8
5 to 6 "	6	0.7
6 to 7 "	13	1.5
7 to 8 "	12	1.4
8 to 9 "	3	0.4
9 to 10 "	7	0.8
Unknown	43	5.1
Total	849	100.0

Symptomatology. In a great many cases there may be a history of previous gastrointestinal symptomatology, such as constipation and indigestion, not related to tuberculosis of the intestine—these being followed by an insidious train of symptoms due to tuberculous disease with the result that a definite diagnosis is not always possible, and, when finally made, the patient is in an advanced stage of the disease.

Stewart⁵ maintains that the earlier symptoms are usually referable to small-bowel lesions, the later symptoms to disease of the large bowel. According to this author, nervousness, slight impairment of appetite, and constipation beyond usual, constitute the most common early diagnostic symptoms of intestinal tuberculosis. Archibald found that constipation is a special symptom of ulceration of the small bowel, while diarrhea is an indication of disease of the large bowel. Alternating diarrhea and constipation, he thinks, indicate ulceration in both tracts.

Table VI shows the relative frequency of the various symptoms of intestinal tuberculosis observed in the Bureau cases.

Methods of Diagnosis. Erickson⁴ maintains that the frequency of the occurrence of intestinal tuberculosis as a complication of the pulmonary form is quite out of proportion to the frequency of its diagnosis. Stewart⁵ holds that intestinal involvement does not necessarily begin with the far-advanced stage of pulmonary tuberculosis. Failure to recognize this complication earlier reflects the

inadequacy of our present diagnostic methods, and the necessity and value of the roentgenologic diagnostic technique as developed by Brown and Sampson.⁶

TABLE VI.—SYMPTOMS OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Tenderness or colicky pain in abdomen . . .	581	68.4
Loss of weight	505	59.5
Gas formation	470	55.4
Impairment of appetite	460	54.2
Discomfort after meals	381	44.9
Diarrhea	334	39.3
Emaciation	329	38.7
Dyspepsia	306	36.0
Alternating constipation and diarrhea . . .	265	31.2
Nausea	261	30.7
Nervousness and irritability	251	29.6
Constipation	231	27.2
Vomiting	207	24.4
Bleeding	49	5.8
Mass formation	34	4.0

Table VII indicates the several diagnostic methods used by the Bureau physicians in detecting intestinal tuberculosis in the group of 849 patients under consideration.

TABLE VII.—DIAGNOSTIC METHOD BY WHICH INTESTINAL TUBERCULOSIS WAS FIRST RECOGNIZED.

	Number of cases.	Per cent.
Roentgen ray, clinical symptoms and physical signs	368	43.3
Clinical symptoms and physical signs	306	36.0
Autopsy	107	12.6
Roentgen ray, alone	65	7.7
Laparotomy	3	0.4
Total	849	100.0

Comparative Value of Various Diagnostic Methods. A study of Table VIII shows that in the examination of 587 patients for tuberculosis of the intestine of the total number under discussion the combined clinical and roentgenologic methods yielded the best results. The disease was definitely diagnosed by these two methods in 389, or 66.27 per cent of the cases.

TABLE VIII.—COMPARATIVE VALUE OF VARIOUS DIAGNOSTIC METHODS.

	Number of cases.	Per cent.
Positive both clinically and by Roentgen ray . . .	389	66.3
Positive clinically and negative by Roentgen ray . .	96	16.3
Positive by Roentgen ray and negative clinically . .	51	8.7
Negative both clinically and by Roentgen ray and in which diagnosis was made at autopsy	48	8.2
Positive clinically but negative by Roentgen ray and at autopsy	2	0.3
Positive by Roentgen ray and negative at autopsy . .	1	0.2
Total	587	100.0

Treatment. In order that treatment may be effective it is essential that an early diagnosis be made and that therapeutic measures be instituted as soon as the condition is recognized. Measures aimed at controlling gastrointestinal symptoms and which result in an improved digestion and assimilation will no doubt benefit the patient and increase his resistance against the progress of both the pulmonary and intestinal tuberculosis.

In the treatment of intestinal tuberculosis rest is most essential; in addition a bland diet, with a minimum amount of roughage, and one which is readily digested and assimilated will help the patient in combating the tuberculous infection.

There are a series of digestive symptoms which are most depressing on the patient and which interfere with his fight against the disease. These require symptomatic medicinal treatment such as calcium chlorid—the latter having been found very helpful, particularly in cases with hyperperistalsis. It seems to act as an antispasmodic when administered intravenously.

When tuberculosis of the bowel is localized and can be eradicated, surgery is the treatment of choice. In resorting to surgery, it is essential that the condition be recognized before it has had an opportunity to spread.

A discussion of the treatment of intestinal tuberculosis would be incomplete without a reference to heliotherapy, both natural and artificial. Many observers have found that heliotherapy is a reliable means of controlling the symptoms of this disease. Erickson⁷ states that the proof of the action of ultraviolet light in tuberculosis is empirical, but that it has a decided effect on the various forms of tuberculosis, possibly through stimulation of the calcium metabolism with a resulting sedative action on the motor mechanism of the intestinal tract. He holds that on this theoretical basis the results of heliotherapy may be divided into two stages; a primary or palliative one as shown by symptomatic relief, and a secondary or curative stage which is evident in the Roentgen ray pictures considerably later.

TABLE IX.—METHODS OF TREATMENT OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Rest	643	75.7
Dietetic	467	55.0
Medicinal	381	44.9
Heliotherapy (artificial)	312	36.8
Calcium chlorid	62	7.3
Heliotherapy (natural)	55	6.5
Surgical	13	1.5
Oxygen therapy	2	0.2

Table IX lists the various regimens used in the Bureau hospitals in the treatment of intestinal tuberculosis. Some of these were in

combination. It is noted that rest, diet, ultraviolet radiation, natural heliotherapy and medicinal therapy including calcium chlorid were the most common therapeutic measures used.

Results of Treatment. Table X indicates the results following the treatment of 849 Bureau patients with intestinal tuberculosis. The statistics point to the fact that treatment is not as hopeless as was formerly believed and that some cases may improve and may even be cured.

It was interesting to learn that of the patients with intestinal tuberculosis who were cured or improved following hospitalization 45.36 per cent showed improvement, arrest or cure of the pulmonic disease while 54.64 per cent of the cases showed a stationary or a retrogression of the pulmonic disease.

TABLE X.—RESULTS OF TREATMENT OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Cured (complete disappearance of clinical symptoms and Roentgen ray signs) . . .	16	1.9
Improved	180	21.2
Unimproved	226	26.6
Worse	67	7.9
Died	360	42.4
Total	849	100.0

Distribution of Intestinal Lesions. It is not always possible to determine the exact location of the tuberculous lesions, inasmuch as the disease may be present in a number of portions of the small and large intestines.

The data contained in Table XI were obtained by clinical and roentgenologic means and at postmortem, and show the relative frequency of the tuberculous lesions in the different portions of the small and large intestines.

TABLE XI.—DISTRIBUTION OF LESIONS OF INTESTINAL TUBERCULOSIS
IN 849 BUREAU PATIENTS.

Location.	Number of cases.	Per cent.
Cecum	444	52.3
Ileum	328	38.6
Ascending colon	271	31.9
Transverse colon	170	20.0
Ileocecal valve	126	14.8
Descending colon	96	11.3
Jejunum	70	8.2
Appendix	64	7.5
Duodenum	50	5.9
Rectum	31	3.7
Sigmoid	21	2.5
Peritoneum	72	8.5
Large portion of intestinal tract	28	3.3

Foci of Infection of Intestinal Tuberculosis. Ulcerative intestinal tuberculosis is almost always secondary to tuberculosis of the lung. The hyperplastic variety is usually a primary infection. In a small percentage of cases foci of infection are found in organs other than the lungs. These findings are shown in Table XII. It is noted that there were 879 foci of infection in 849 cases; that is, there was more than one focus of infection in certain of the cases.

TABLE XII.—FOCI OF INFECTION OF INTESTINAL TUBERCULOSIS.

	Number of cases.	Per cent.
Lungs	828	97.5
Bone	14	1.6
Urogenital tract	7	0.8
Abdominal lymph nodes	4	0.5
Pleura	3	0.3
Thoracic lymph nodes	1	0.1
Joints	1	0.1
Other organs	21	2.5
Total	879	

Complications. The pathology of intestinal tuberculosis is primarily one of tubercle formation. After a coalescence of the tubercles there is a tendency to disintegration and multiple ulcer formation. Tuberculous ulcers very seldom perforate due to the fact that there is a tendency to new tissue formation. The end-results of a tuberculous ulcer may be: Stenosis of the bowel with obstruction, or perforation followed by peritonitis. Table XIII indicates the frequency of these complications in 490 cases of the total number studied.

TABLE XIII.—COMPLICATIONS OF INTESTINAL TUBERCULOSIS SHOWING INCIDENCE OF ULCERATION, PERFORATION OR OBSTRUCTION.

	Number of cases.
Ulceration of intestine	453
Perforation of intestine	17
Obstruction of intestine	20
Total	490

Roentgenologic Characteristics of Intestinal Tuberculosis. Brown and Sampson⁶ teach that no moderately or far-advanced case of pulmonary tuberculosis can be assumed to have been thoroughly examined unless a Roentgen ray study of the bowel has been made. This is the only method which will enable one to detect tuberculous involvement of the alimentary tract in its incipency or which will make it possible to exclude the disease at any stage.

There are a number of roentgenologic signs frequently found in this disease, which may also be present in nontuberculous conditions of the alimentary tract, but when found in a case of pulmonary or

extrapulmonary tuberculosis the probabilities are that the condition is one of intestinal tuberculosis.

Table XIV indicates the relative frequency of the various roentgenologic signs of intestinal tuberculosis encountered in the group of Bureau cases.

TABLE XIV.—ROENTGENOLOGIC CHARACTERISTICS OF INTESTINAL TUBERCULOSIS IN A GROUP OF 849 BUREAU PATIENTS.

	Number of cases.	Per cent.
Filling defects in cecum and ascending colon	312	36.7
Irregularity of outline of cecum and loss of haustral segmentation of ascending colon	251	29.6
Hypermotility at six hours	219	25.8
Hypermotility at twenty-four hours	216	25.4
Filling defects in portions of large intestine other than cecum and ascending colon	145	17.1
Ileal stasis with delay in filling the cecum	112	13.2
Roentgen ray changes noted by enema	37	4.4
Fixation of cecum	27	3.2

The Clinical Laboratory as an Aid in Diagnosis. On account of the vague symptomatology of intestinal tuberculosis it is necessary to employ any diagnostic methods which may assist the clinician in the detection of the disease. The usefulness and importance of the Roentgen ray laboratory in the diagnosis of intestinal tuberculosis has already been commented on. An attempt was also made to ascertain the value of the clinical laboratory in the detection of the disease. Accordingly a study was made of the various laboratory methods used in the examination of a group of 527 Bureau patients. The result of the study may be seen by referring to Table XV.

It would appear that clinical laboratory findings do not offer very much assistance in the detection and early diagnosis of intestinal tuberculosis. Even in those cases in which tubercle bacilli are found in the feces it is probable that the organisms have their origin in the sputum.

TABLE XV.—CLINICAL LABORATORY DIAGNOSIS OF INTESTINAL TUBERCULOSIS.

	Number of cases.
Tubercle bacilli in feces with tubercle bacilli also in sputum	84
Increase of number of monocytes in blood	65
Blood (occult)	56
Blood (gross)	50
Tubercle bacilli in feces with no tubercle bacilli in sputum	8
No clinical laboratory signs	264
Total	527

Cause of Death. Death of cases of intestinal tuberculosis is due to the spread of the intestinal or pulmonic disease or to a complication of some kind, such as peritonitis, perforation, or meningitis.

There were 360 deaths in the series of 849 cases under consideration. The various causes of death may be noted by referring to Table XVI.

TABLE XVI.—CAUSE OF DEATH.

	Number of cases.	Per cent.
Extension of intestinal or pulmonic tuberculous disease	314	87.2
Tuberculous peritonitis	13	3.6
Intestinal obstruction	12	3.3
Intestinal perforation	9	2.5
Tuberculous meningitis	2	0.6
Hemorrhage of intestines	1	0.3
Other causes	9	2.5
Total deaths	360	100.0

Lesions of Intestinal Tuberculosis as Seen at Autopsy. In order to ascertain the effect of various therapeutic measures upon the lesions of intestinal tuberculosis as seen at autopsy, a study was made of the material in a series of 236 postmortem examinations out of a total of 360 Bureau patients dying from intestinal tuberculosis. The results of this study may be noted by referring to Table XVII.

TABLE XVII.—INTESTINAL LESIONS AS SEEN AT AUTOPSY.

	Untreated.	Treated by rest and diet.	Treated by helio- therapy.	Treated by rest, diet and helio- therapy.	Total.
Active ulceration	14	113	12	8	147
Some active ulcers, others healed	1	22	13	3	39
Complete healing of all ulcers	1	...	1
Regeneration of epithelia	9	4	...	13
Flattening of ulcer walls	5	3	...	8
Mammillation	8	4	...	12
Fibrosis	4	9	2	1	16
Total	19	166	39	12	236

Duration of Treatment by Rest and Diet of Cases Coming to Autopsy. Table XVIII indicates the various periods of treatment of patients with intestinal tuberculosis who died and who came to autopsy. It also indicates the types of lesions found after treatment by rest and diet.

Duration of Treatment by Heliotherapy of Cases Coming to Autopsy. Table XIX indicates the duration of treatment of Bureau patients receiving ultraviolet radiation who died and who came to autopsy.

The data in Table XVIII and XIX would seem to indicate that ultraviolet radiation, either alone or in combination with a rest and diet regimen, does not yield results to prove that it has specific healing action upon tuberculous disease of the intestines. This is

the view held by a number of observers, notably Smithies,⁸ who maintains that he is not yet ready to subscribe to the opinion that heliotherapy has any curative influence whatever on the lesions of intestinal tuberculosis. In his experience the study of the pathologic specimens showed such a great variation in the character of bowel lesions and the efforts at resistance that it was difficult for him to prove and to believe that healing actually resulted from heliotherapy. Brown and Sampson⁶ hold that inasmuch as a few cases of intestinal tuberculosis recover without any treatment whatever, judgment of the true value of ultraviolet radiation and natural heliotherapy is difficult to make.

TABLE XVIII.—DURATION OF TREATMENT OF CASES COMING TO AUTOPSY WHO HAD BEEN TREATED BY REST AND DIET.

	Active ulceration.	Some active ulcers, others healed.	Regeneration of epithelia.	Flattening of ulcer walls.	Mammillation.	Fibrosis.	Total.
Less than 1 month	35	7	3	..	3	3	51
1 to 3 months	38	9	3	..	2	3	55
4 to 6 "	23	4	2	..	2	2	33
7 to 12 "	11	3	3	1	2	2	22
1 to 2 years	10	3	1	..	1	1	16
Over 5 "	1	1
Total . . .	118	26	12	1	10	11	178

It is, therefore, reasonable to infer that heliotherapy has a beneficial effect upon tuberculous disease of the intestines, whether or not it may result in a cure of the disease is questionable.

TABLE XIX.—DURATION OF TREATMENT OF CASES COMING TO AUTOPSY WHO HAD BEEN TREATED BY HELIOTHERAPY.

	Active ulceration.	Some active ulcers, others healed.	Complete healing of all ulcers.	Regeneration of epithelia.	Flattening of ulcer walls.	Mammillation.	Fibrosis.	Total.
Less than 1 month	2	2
1 to 3 months	8	2	..	2	2	2	..	16
4 to 6 "	9	9
7 to 12 "	4	5	..	2	2	2	..	15
1 to 2 years	2	5	1	1	9
Total . . .	25	12	1	4	4	4	1	51

Summary and Conclusions. 1. On account of the vague clinical symptoms and signs of intestinal tuberculosis it is difficult to ascer-

tain definitely the exact incidence of the disease as a complication of pulmonary tuberculosis. However, in a series of 200 autopsies of Bureau patients dying from pulmonary tuberculosis, it was found that 60.5 per cent showed evidence of a coëxisting intestinal tuberculosis.

2. Of a series of 849 Bureau beneficiaries hospitalized for intestinal tuberculosis, it was found that the largest number were under observation for various periods up to one year; the next largest number were under observation from one to two years.

3. Of the Bureau patients with intestinal tuberculosis, 93.95 per cent had pulmonary tuberculosis which was classified as far advanced according to the schema of the American Sanatorium Association. Furthermore, 82.4 per cent of the group had tuberculous lesions with cavitation, while 77.6 per cent had bilateral lesions with more than one-third of the better lung involved. The majority of the patients had either exudative lesions or a combination of exudative and fibrotic lesions.

4. The period of time between the diagnosis of pulmonary tuberculosis and the detection of the intestinal complication varied considerably—the largest group showed evidence of intestinal tuberculosis from one to three years after the diagnosis of pulmonary tuberculosis was made.

5. The symptoms of onset of intestinal tuberculosis are vague, so that in many instances it is difficult to diagnose the condition. In the series studied it was found that the largest group gave evidence of intestinal tuberculosis from one to six months before a definite diagnosis was made; the next largest group had symptoms of this condition from seven to twelve months before it was definitely detected. In a number of cases the symptoms of onset existed from one to ten years before a definite diagnosis was made.

6. The most frequent symptoms were: Tenderness or colicky pain in abdomen, loss of weight, gas formation, impairment of appetite, discomfort after meals, diarrhea, emaciation, dyspepsia, alternating constipation and diarrhea, nausea, nervousness and irritability.

7. The diagnosis of intestinal tuberculosis was definitely made in 43.3 per cent by both clinical and Roentgen ray methods; in 36 per cent a diagnosis was made clinically; in 7.7 per cent by a roentgenologic examination; and in 12.6 per cent a diagnosis was not made either clinically or by Roentgen ray but the disease was found at autopsy. In attempting to ascertain the superiority of the various diagnostic methods it was found that the largest number of cases of intestinal tuberculosis was positively diagnosed by both clinical and Roentgen ray means.

8. The most frequent therapeutic regimens used in the Bureau cases in the treatment of intestinal tuberculosis were: Rest, diet,

heliotherapy, both natural and artificial, and medicinal therapy including calcium chlorid.

9. Of the total number of 849 patients with intestinal tuberculosis approximately 21 per cent were improved and approximately 2 per cent were cured, following hospitalization; the rest of the patients were unimproved or were in a condition of retrogression; 42.4 per cent of the patients died. It is thus seen that treatment is not altogether hopeless, as is commonly believed. Some cases may improve and may even be cured following various therapeutic procedures.

10. The most frequent sites of the lesions of alimentary tuberculosis, in the order named, were: Cecum, ileum, ascending colon, transverse colon, ileocecal valve, descending colon, jejunum, appendix, duodenum, rectum and sigmoid. There was involvement of the peritoneum in 8.5 per cent; and 3.3 per cent showed the presence of tuberculous lesions throughout a large portion of the intestinal tract.

11. While the majority of cases of intestinal tuberculosis are almost always secondary to pulmonic disease, in a small percentage of cases foci of infection are found in organs other than the lungs. The most frequent foci of infection of the cases studied were in the: Lungs, bone, urogenital tract, abdominal lymph nodes and pleura.

12. More than half of the cases of intestinal tuberculosis had some complication, such as ulceration, perforation, or obstruction. The most common complication was ulceration of the bowel.

13. The most frequent Roentgen ray signs characteristic of intestinal tuberculosis in the order named, were: Filling defects in cecum and ascending colon, irregularity of outline of cecum and loss of haustral segmentation of ascending colon, hypermotility at six hours, hypermotility at twenty-four hours, filling defects in portions of the large intestine other than in the cecum or ascending colon, ileal stasis with delay in filling the cecum, Roentgen ray changes noted by enema and fixation of cecum.

14. In reviewing the clinical laboratory findings in the group of cases under consideration, it was found that these do not offer very much assistance in the detection and the early diagnosis of intestinal tuberculosis. Even in those cases in which tubercle bacilli are found in the feces it is probable that the organisms have their origin in the sputum.

15. Death of cases of intestinal tuberculosis is due to a spread of the tuberculous infection, or to a complication of some kind, such as peritonitis or meningitis. In the majority of the Bureau cases the cause of death was an extension of the intestinal or the pulmonic disease.

16. Of a series of 236 cases treated by various regimens, who came to autopsy, the majority received routine sanatorium treatment; a small number of the cases received ultraviolet radiation either alone

or in combination with rest and diet. After treatment by the various methods it was found that most of the cases showed the presence of active ulcers at autopsy. A small number showed ulcers which were both active and healed.

A review of the statistical data would lead one to state that ultraviolet radiation, either alone or in combination with rest and a dietetic regimen, had a beneficial effect upon intestinal tuberculosis; but it is questionable whether or not it may lead to a cure.

NOTE.—It is desired to acknowledge the encouragement of the Medical Director of the U. S. Veterans' Bureau in this study, and of the medical officers in the field who were kind enough to furnish the data which form the basis of this paper. It is also desired to acknowledge the assistance rendered by Miss Anne Bambery, Statistical Assistant in the Research Subdivision.

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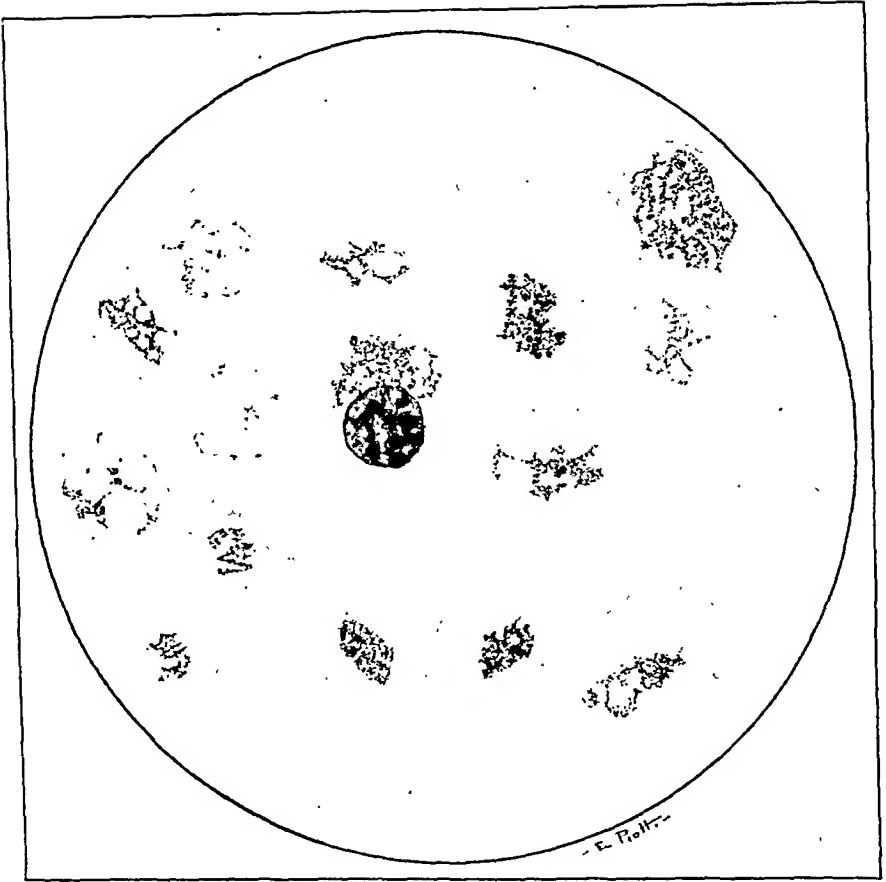
A CASE OF CONGENITAL HEMOLYTIC JAUNDICE WITH AN UNUSUALLY HIGH PERCENTAGE OF RETICULOCTES.

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AN increase in the reticulocytes in the peripheral blood as a feature of chronic congenital and acquired hemolytic jaundice was recognized originally by Chauffard in 1907. Meulengracht¹ in his excellent monograph "Der chronische hereditäre hämolytische Icterus" reported reticulocyte counts of 20 to 30 per cent, and many authors (Krumbhaar,² Lucas,³ Piney,⁴ Tileston,⁵ and others) have given similar figures in each type, the higher percentages tending to occur in the acquired form and during periods of exacerbation of the icterus. Unusually high percentages of immature erythrocytes have not been reported as occurring during the course of either acquired



Drawing from blood smear stained with brilliant cresyl blue and Wright's stain
Reticular material is present in the majority of the cells.

or congenital chronic hemolytic jaundice, although Reynolds⁶ obtained counts of 95 per cent in a case of the acquired type in a young adult. Thus we wish to record a case of congenital hemolytic jaundice in which the blood at different times showed extremely high reticulocyte counts.

Case Report. A white male child, aged three years, was referred to this hospital on May 26, 1926, because of jaundice since birth. There was no history of jaundice having occurred in other members of the family. The father, mother and one sibling were living and well. One child had died at the age of eleven months of pneumonia. The patient had had slight jaundice constantly, with exacerbations associated with acute infections. During the two years previous to entry he had been given hospital care in a neighboring city on three occasions because of jaundice and weakness, closely following the onset of an acute upper respiratory infection characterized by coryza, slight cough, irritability and fever. Each time he showed nonobstructive jaundice of a severe degree, slight generalized lymph-node enlargement, an enlarged spleen and secondary anemia. The anemia had been very severe and transfusion of blood had been given on two occasions, followed each time by distinct improvement in the patient's general condition. The jaundice had gradually diminished as the acute infections subsided.

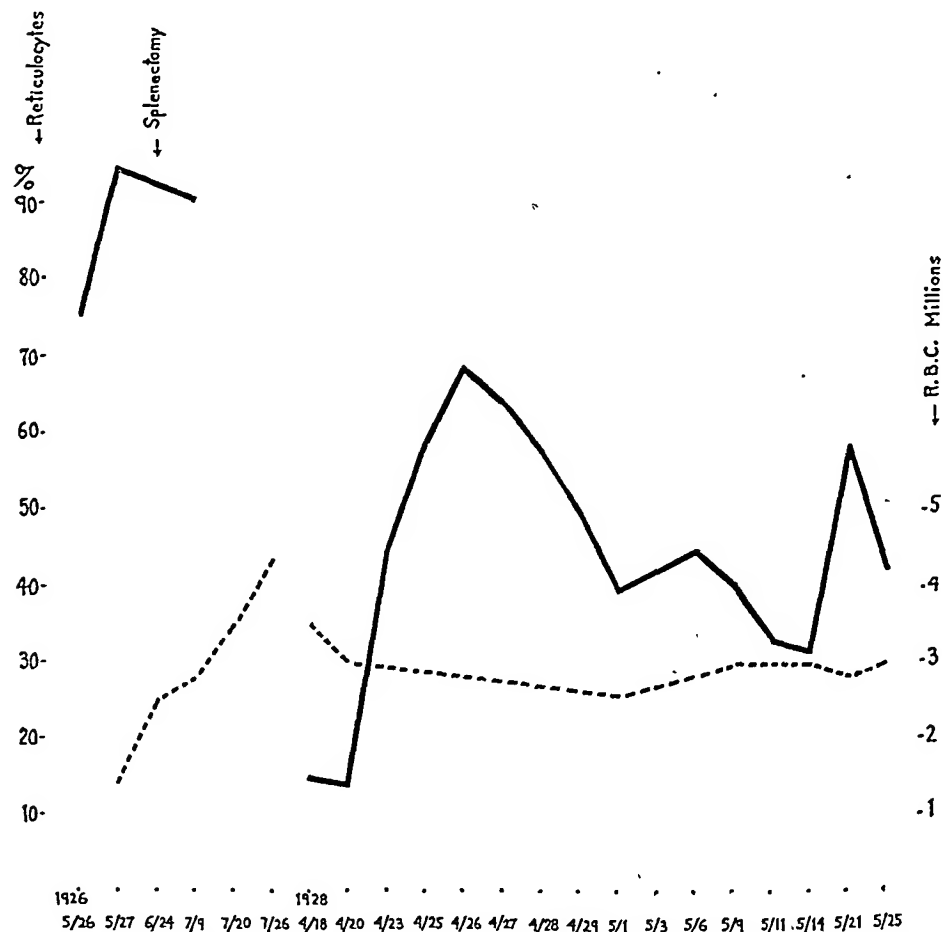
When the patient was first seen in this Clinic there was intense icterus of the skin and sclerae. The liver and spleen were both very large, the former extended 5 and the latter 7 cm. below the costal margin. The spleen was firm and not tender. There was slight generalized enlargement of the lymph nodes and the tonsils were big and cryptic. Other physical findings were essentially normal. The red blood cells numbered 1,200,000 per c.mm. with 30 per cent hemoglobin. When stained with brilliant cresyl blue, 92 per cent of the erythrocytes were found to contain reticular material and occasional cells with nuclei and nuclear bodies were seen. There was a moderate leukocytosis and the platelets appeared normal. The urine gave positive reactions for bile and urobilin. Two fragility tests were interpreted as normal, but a third showed very definite decrease in resistance of the erythrocytes to hypotonic saline solutions. Fragility test, May 27, 1926: hemolysis began in 0.44 per cent saline solution, complete in 0.20 per cent. May 28: hemolysis began in 0.42 per cent, complete in 0.20 per cent. June 10: hemolysis began in 0.68 per cent complete in 0.52 per cent.

The diagnosis of congenital hemolytic jaundice was, therefore, established and two weeks after entry the spleen was removed. The weight was 190 gm. The capsule was thickened and covered with fibrous adhesions over the lower medial surface. The organ was firm in consistency; the cut surface homogeneous and deep red. Microscopic examination revealed a diffuse increase in fibrous tissue in the capsule and trabeculae and to an even greater degree in the walls of the venules. The sinuses were for the most part empty. There were scattered small groups of myelocytes and nucleated erythrocytes. The corpuscles were numerous; many were large with active germinal centers while others were small and inactive. Diagnosis: splenomegaly with fibrosis and hemopoietic activity.

The patient made an uneventful postoperative recovery with gradual general improvement and was discharged home two months later, a sub-icteric tint persisting in the skin and sclerae. Following splenectomy, the erythrocytes and hemoglobin rose to 4,500,000 and 70 per cent respectively and the reticulocytes remained about 90 per cent. Two fragility tests on the red blood cells were normal, hemolysis beginning in 0.40 per cent saline solution and complete in 0.30 per cent. The results of these tests, however,

may have been altered by the large number of reticulocytes present since these immature cells are considered to be more resistant to hypotonic saline solutions than the adult forms.

During the next twenty months he seemed much better. However, slight jaundice persisted and mild exacerbations occurred on several occasions following acute upper respiratory infections. He was readmitted to the Hospital in April, 1928, ten days after the onset of such an infection and remained seven weeks. During this time the infected tonsils were removed in an effort to lessen the frequency of the recurring "colds."



Solid line, reticulocytes; broken line, erythrocytes. Showing the persistent elevation of reticulocytes during the two periods of observation.

While in the hospital he showed persistent jaundice of a varying degree. The erythrocytes remained about 3,000,000 per c.mm. and the hemoglobin between 30 and 50 per cent. The leukocyte counts were practically normal with occasional moderate rises. There was a normal to increased number of blood platelets at each examination. The bleeding and clotting times were normal. Fragility tests on the red blood cells were normal. On two occasions, hemolysis began in 0.52 per cent saline solution and was complete in 0.30 per cent, while normal controls showed hemolysis from 0.50 to 0.36 per cent saline. Urobilin was frequently present in the urine in excessive amounts. The reticulocytes at the time of this second admission were 15 per cent. There was a rapid unexplained rise to 70 per cent on

the ninth day in the Hospital and they remained between 30 and 65 per cent until the patient was discharged (chart).

Comment and Summary. The striking feature of this case of congenital hemolytic jaundice is the unusually high percentage of reticulocytes present over a long period of observation. The reports in the literature indicate that the number of immature cells occurring during the course of congenital or acquired hemolytic jaundice rapidly returns to normal following splenectomy. Two years after removal of the spleen the blood of this patient showed reticulocyte counts of 30 to 70 per cent. Although improved, he had not been cured by the operation, and the persistent increase in the percentage of immature red blood cells may be interpreted, together with the persistence of jaundice and anemia and the occurrence of hemolytic crises, as additional indication of continued activity of the disease process.

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A CASE OF ACQUIRED HEMOLYTIC JAUNDICE WITH UNUSUAL FEATURES AND IMPROVED BY SPLENECTOMY.

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THE following case is recorded on account of certain unusual features in the clinical picture and laboratory findings, and because of the striking improvement after splenectomy. The patient had an exceedingly large number of reticulocytes in the peripheral blood, only a slight alteration in the fragility of his red blood cells to hypotonic salt solution, and was very deeply jaundiced.

Case Report. E. M. (No. 276495). A single, American, market clerk, aged twenty-one years, was admitted to the Massachusetts General Hospital on May 24, 1926, complaining of weakness and jaundice. He had been well

until seventeen months before admission, when he was seized with a severe cough, accompanied by headache, general malaise, slight chills and a mild degree of fever. He went to bed and at the end of a week he noticed that his skin and scleræ had become yellow and that his urine was of a dark amber and his stools of a dark yellow color. There was no appreciable change in his condition after he had been in bed three weeks, and, although the jaundice and weakness had persisted, he returned to work.

From that time until his admission to the hospital, sixteen months later he was never free from jaundice, but he observed that its intensity varied greatly from time to time. When the icterus was more marked he was dyspneic on slight exertion and too weak to work, while at other periods there was only slight jaundice, and he was able to carry on his regular activities in spite of becoming easily fatigued. Throughout these months he continued to pass dark-colored urine, while his stools always appeared to him normal in color. Two months prior to admission he became more deeply icteric than ever before and so weak that he was forced to return to bed, where he remained until he was brought to the hospital. His appetite had been excellent despite the jaundice, but he lost nearly 25 pounds of weight during his illness.

The patient's past history was entirely negative. He had lived in New Hampshire all his life and had never had any illnesses except measles and mumps. Both of his parents, three brothers and two sisters were living and well, and there was no family history of jaundice, anemia or other familial disease.

Physical Examination. Physical examination showed a well-developed and moderately nourished young man whose skin and scleræ were extremely icteric. The temperature, pulse and respirations were normal. The mucous membranes were extremely pale. The eyes, ears, teeth, nose, throat, lymph nodes, thyroid and lungs presented no abnormalities. The heart was slightly enlarged to the left, and a loud blowing systolic murmur was heard at the mitral area. The abdomen was rather prominent, and the liver was easily palpable 4 cm. below the costal margin, while the spleen could be felt at about the same level in the abdomen. Both of these organs were thought to be smooth, firm and slightly tender on palpation. There was no evidence of fluid in the abdominal cavity, no edema of the extremities and the tendon reflexes were normal.

The Blood. On admission the red blood cell count was 1,500,000 per c.mm. and the hemoglobin was 40 per cent. The red blood cells were characteristic of a marked secondary anemia, with evidence of an extraordinary degree of regeneration. There was a great variation in the size of the cells, with a moderate degree of achromia and a slight variation in shape. Almost every cell was polychromatophilic, some staining much more deeply than others. Two or 3 nucleated red blood cells were seen in each oil immersion field of the microscope. A specimen stained with brilliant cresyl blue showed reticular material in 95 per cent of the red blood cells.

The total white blood cell and differential count were essentially normal, and the blood platelets appeared to be slightly decreased.

In a test of the fragility of the red blood cells there was partial hemolysis in 0.4 per cent aqueous solution of sodium chlorid and complete hemolysis in 0.32 per cent solution, and identical results were obtained in a control of normal blood.

The icteric index of the patient's serum was 100, and a qualitative van den Bergh gave a negative direct and a strongly positive indirect test.

Blood coagulation time, bleeding time, blood Wassermann, blood calcium and phosphorus were normal and there was no autoagglutination of the red blood cells.

Other Examinations. The basal metabolic rate was +25 per cent. Several stools were examined and all were of normal consistency, dark brown in color and showed no evidence of blood either microscopically or by the guaiac test. The urine was dark amber in color at all examinations and acid in reaction. Its specific gravity varied from 1.014 to 1.022. No albumin, sugar or bile was detected by the routine tests, and the sediment was consistently negative. No Bence-Jones protein was found and only a trace of urobilin. The high color was thought to be due to the presence of urates. Gastric analysis and roentgenologic examination of the long bones showed no variation from the normal, and Roentgen rays of the gall bladder region showed no evidence of cholelithiasis.

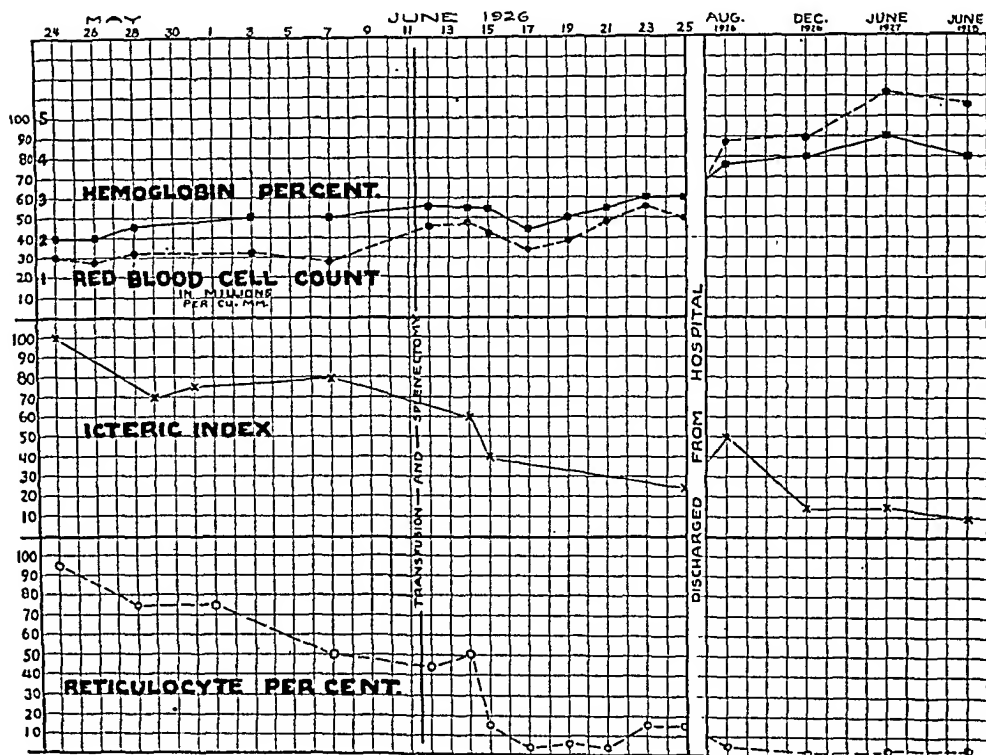


FIG. 1.—Synopsis of Blood studies.

Clinical Course. During the first two weeks of the patient's stay in the hospital the intensity of the icterus was observed to vary considerably from time to time, and there was a corresponding variation in the number of reticulocytes found in the blood stream, but there was otherwise no notable change in his condition. Two and a half weeks after admission he was given a transfusion of 500 cc. of whole blood and splenectomy was performed by Dr. Beth Vincent. At operation the liver appeared essentially normal, although somewhat enlarged and slightly congested. The gall bladder was full and distended, but not acutely inflamed. The spleen was about four times the normal size, soft, dark red in color and its external surface presented two areas of depression, which were thought to indicate old infarctions. There were a few adhesions to the diaphragm, but the spleen was removed without difficulty. The pathologic department made the diagnosis of "splenic hyperplasia." The patient had a normal and brief postoperative convalescence, and was discharged from the hospital two weeks after operation.

The chart on page 551 shows, in graphic form, the striking decrease in icterus and in the reticulocytes, with a corresponding rise in the concentration of the hemoglobin and red blood cells.

The patient returned to work three months after splenectomy and has been at work daily since then. He rapidly regained weight and strength, and, although laboratory tests have continued to show a slight degree of icterus, he has been clinically free of symptoms for three years.*

The fragility of the red blood cells, which was normal at the time of his admission to the hospital, has been tested several times since splenectomy and the results have been variable. At certain examinations their fragility to hypotonic salt solution has been normal and at others slightly increased. At no time have his red blood cells been definitely abnormally fragile.

Discussion. This case presents certain features that are not typical of acquired hemolytic jaundice. The marked degree of icterus, the extremely large number of immature red blood cells in the peripheral blood, and the essentially normal fragility of these corpuscles are all findings that are not noted in the textbook descriptions of the disease. It is known that acquired hemolytic jaundice is more apt to be atypical than the congenital or familial type, and there are, perhaps, reasons for the appearance of the unusual features that this patient presented.

This case was obviously one of unusual severity, even allowing for the fact that the acquired form of hemolytic jaundice is commonly more severe than the congenital type. It seems reasonable to assume that the intense icterus was dependent upon an unusual degree of blood destruction. The extraordinary number of reticulocytes in the blood stream may be regarded as evidence of a maximal response on the part of the bone marrow to compensate for the marked degree of blood destruction.

The fragility of the red blood cells in hemolytic jaundice is classically increased. Indeed, many authorities regard this as the fundamental pathologic basis of the disease. It is, therefore, difficult to account for the essentially normal fragility of this patient's red blood cells. Some investigators believe that immature red blood cells, at least in certain disorders of the blood, are more resistant to hemolysis by hypotonic sodium chlorid solution than are the adult cells, while others hold that this is not the case. New experimental studies concerning this matter are desirable. If, however, the first view is correct, it is conceivable that the large number of reticulocytes found in this case have obscured the fact that the mature red blood cells were abnormally fragile.

* The last blood examination was made on July 16, 1929, and is not recorded in the accompanying chart. At that time the hemoglobin was 85 per cent; the red blood cell count, 5,400,000 per c.mm. The red blood cells were normal in appearance and the total white blood cell and differential counts were normal. A specimen stained with brilliant cresyl blue showed 0.9 per cent reticulocytes. In a test of the fragility of the red blood cells there was partial hemolysis in 0.4 per cent aqueous solution of sodium chlorid and complete hemolysis in 0.25 per cent solution. The icteric index of the serum was 5.

Finally, it is of interest to note that removal of the patient's spleen has apparently resulted in a clinical cure, whereas, in another case of hemolytic jaundice with an unusually high percentage of reticulocytes the same procedure has been of but temporary and far less definite benefit.

Summary. A young man, entering the hospital after seventeen months of continuous jaundice, presented a marked icterus and a considerable degree of secondary anemia with unusually active blood regeneration. A diagnosis of acquired hemolytic jaundice was made and splenectomy was performed with striking improvement in the icterus, the anemia and the patient's general condition. Three years after operation the patient appears to be clinically well.

REVIEWS.

THE ESSENTIALS OF HISTOLOGY. By SIR EDWARD SHARPEY SCHÄFER, F.R.S., Professor of Physiology in the University of Edinburgh. Twelfth edition. Pp. 628; 758 illustrations. Philadelphia: Lea & Febiger, 1929. Price, \$5.00.

FROM its first publication, this work has been a standard among the textbooks in its field. The present edition has been completely revised and numerous new illustrations have been added in the form of photographs.

The book has been written for the use of students and like the previous editions, it will be one of the best guides to histology that is anywhere available.

Each chapter of histology has been completely covered, giving the students complete information about the structure of tissues and organs and the development of them. It is sufficiently elementary to be used by students yet complete enough for the use of advanced workers as a key to the interpretation of larger works.

G. R.

THE NORMAL AND PATHOLOGICAL PHYSIOLOGY OF BONE: ITS PROBLEMS. By R. LERICHE and A. POLICARD. Pp. 236; 33 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, \$5.00.

IN a terse but frequently involved manner Leriche and Policard present much data, a few facts, many opinions and a wealth of hypothesis concerning the physiology and pathology of bone. This treatise, while stimulating, leaves one with a feeling of regret that the procedures of their experiments are not given in sufficient detail to permit the reader to draw his own conclusions. It is one thing to speak with authority from incontrovertible proof and another to so speak without the presentation of proof for statements made.

The monograph warrants a careful and unbiased study, as it is controversial; it has been well received and most favorably reviewed. In all likelihood this work will supply the stimulus for intensive investigations by other workers.

The illustrations, while chiefly diagrammatic, are good; the footnote comments of the translators are pertinent.

G. W.

THE LAYMAN LOOKS AT DOCTORS. By S. W. and J. T. PIERCE.
Pp. 251. New York: Harcourt, Brace & Co. Price, \$2.00.

It is a great pity such a book as this was ever published. It will not hurt the medical profession but I think that it is capable of doing much harm to the reading public. The book is little else than the popularizing of Freudian psychoanalysis, and the description of the lady's difficulties, though very incomplete from a clinical point of view, nevertheless gives one the impression that she is a cyclothymic individual and that she is suffering from a depression with suicidal impulses. That this depression had to run its course and that it was fortunate for psychoanalysis that she tried it at the end instead of at the beginning of her illness, is of course evident. The description of her experiences at the various sanatoria does not ring true, but reminds one very strongly of the stories that psychotics are inclined to tell of their experiences during an attack, even to the point of giving all the credit for their recovery to the hospital, or the doctor, or the particular form of treatment which they were undergoing when it took place.

As is well known, there is no method of treatment yet discovered that changes the periodicity of manic depressive episodes, or that materially shortens the attacks. The best that any of us has been able to do is to modify these attacks through building up the insight of the patients so as to avoid unnecessary mental and physical strain, and as far as possible insuring the greatest possible physical and mental normality by daily activities. It is only those who have gained insight who do not identify their symptoms and the fact that they do not get well immediately with the treatment they are receiving during the attack; and likewise it is only those who have gained insight who do not credit some coincidental circumstance with their recovery. The patient retails experiences in sanatoria, presumably for mental diseases, run by the old-time custodial type of psychiatrist who is fortunately becoming rare, or in the so-called Nursing Homes run by faddists or general practitioners. If the lady had hysteria she was out of place in either type described; if she had a mental disease, as I believe she had (if her account is genuine), then she was in the right place to begin with, though unfortunately under the least skilled and poorest type of psychiatrist available. Nevertheless, I believe if she had remained in the first hospital that she would have recovered there at approximately the same date that she did under the psychoanalyst.

The book is dangerous and liable to do harm because, as first explained, psychoanalysis should not get the credit. This method may be of some benefit, but only in qualified hands and only when applied to a very restricted type of case. I have had an occasional psychasthenic who was said to have been benefited by this treatment; on the other hand, it has been my sad experience to see many cases

which have been distinctly harmed by it. So, to have a book go forth which recommends, apparently from the unprejudiced point of view of a layman, psychoanalysis as a universal panacea, I believe to be a great pity.

It is unfortunate that the word psychoanalyst has come to mean Freudian analysis; for of course the constructive and synthetic means of reëducation or any other rational treatment of mental disorders must be based upon the analysis of the mental and emotional make-up of each patient, as well as the environmental elements and problems which are in his life. In many cases a profound and exhaustive analysis is not necessary; but in many others the crux of an individual's difficulty is much more subtle, much less easily recognized, perhaps, by him, and then the research must necessarily be a more thorough affair. It is quite true that a rational analysis as a basis of reëducation is not only desirable but necessary. However, tracing a claustrophobia to infantile impressions received during parturition, as is done in this book, is a typical absurdity of the Freudian School and one that a reasonably good neurologist or anyone with the slightest familiarity with embryology could not make. The truth is that the Freudians are for the most part plainly maladapted individuals and thoroughly uncontrolled thinkers. A. R.

THE MEDICAL MUSEUM. BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M. AND H. Pp. 172; 44 illustrations. London: The Wellcome Foundation, Ltd.

THIS book is not merely a theoretical contribution to the improvement of museums in general and medical museums in particular, but a description of practical achievement.

The author is precise, clear and has obviously devoted much study, skill and care to a subject on which this book stamps him as an expert. Having in the first chapter discussed the functions of a medical museum and made a plea for reform and for a wider outlook, Dr. Daukes proceeds in subsequent chapters to describe and discuss the details of the new system of visual teaching on which the ideal medical museum is based.

This is followed by appendices dealing with the application and development of the system, with types of buildings, walls, screens, cases, labels, illustrations and technical details of preserving and mounting specimens. In conclusion there is a valuable and complete bibliography of technical museum publications and 45 whole-page illustrations of screens, sections and specimens which are most helpful as providing practical evidence of the soundness and practicability of this new system of visual teaching. W. F.

THE NUTRITION OF HEALTHY AND SICK INFANTS AND CHILDREN.
By E. NOBEL, PROF. C. PIRQUET and P. WAGNER. Translated
by BENJAMIN M. GASUL, B.S., M.D. Second revised edition.
Pp. 243; 78 illustrations. Philadelphia: F. A. Davis Company,
1929. Price, \$3.50.

THIS translation brings the ingenious nutritional system of the recently deceased von Pirquet to the attention of the English speaking physician. Couched in excellent English idiom, clear and brief in explanation, it renders understandable this system so noted for its complicated, symbolic terminology.

The first part of the book considers the theoretical aspects of nutrition, the properties of the food elements and the nutritional requirements of children as computed by the "nem" system.

The second part is devoted to the practical aspects of the same subject, both for normal and for sick children. The diarrheal disorders are very simply classified as acute mild, acute severe, chronic mild and chronic severe. There is a very excellent discussion of the subject of food tolerance and a presentation of its principles by charts. This is a subject highly stressed by the authors, but very briefly dismissed in almost all American books on infant feeding. Nutritional management is outlined in infectious, nervous and metabolic diseases such as nephritis, pertussis, enuresis and diabetes.

Finally, there are about 38 pages of recipes, formulas and diets which the reviewer feels are in themselves sufficient reward for his reading.

J. S.

CORONARY THROMBOSIS: ITS VARIOUS CLINICAL FEATURES (MEDICINE MONOGRAPH XVI). By SAMUEL A. LEVINE, M.D. Pp. 178; 85 illustrations. Baltimore: The Williams & Wilkins Company, 1929. Price, \$3.00.

It is only in recent years that it has been possible to separate the coronary thrombosis syndrome during the life of the patient from that of angina pectoris. Though energetically studied and written upon, the subject has not hitherto been comprehensively treated. It is an appropriate service, therefore, for the Medical Monograph Series to fill the gap and the task has been well done by Dr. Levine, himself an important contributor to the field. A conventional form of treatment is followed (General considerations, etiology, symptoms diagnosis, prognosis, treatment and so forth). Pathologic considerations—a term apparently confused with morbid anatomy—are curiously placed between treatment and the large section devoted to case reports. Every up-to-date internist should familiarize himself with the contents of this book.

E. K.

GASTRIC AND DUODENAL ULCER. By ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., and MATTHEW J. STEWART, M.B. (GLASGOW), F.R.C.P. Pp. 544; 159 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$20.00.

THE authors have covered their subject in a most thorough, scientific and painstaking manner. Peptic ulcer is discussed from every standpoint, including anatomy, physiology, symptomatology and pathologic. A great number of statistical tables aid the reader in forming accurate and helpful conclusions, concerning indications for operation, the results of the various types of surgical procedures employed and the ultimate results both in mortality and morbidity. Many excellent illustrations enhance the value of the text. The line drawings of the radiograms are a distinct help to the beginner as well as the more experienced clinician. There is a surprisingly small page space taken up by poor and ill-chosen reproductions of old cuts. The colored plates are very good and captioned helpfully. The reader has here some five hundred pages of reference, statistics and bibliography that are extremely helpful to him as a teacher, diagnostician and surgeon. E. E.

COMMON INFECTIONS OF THE FEMALE URETHRA AND CERVIX. By FRANK KIDD, M.A., M.CH. (CANTAB.), F.R.C.S. (ENG.) and A. MALCOLM SIMPSON, B.A., M.B., D.P.H. (CANTAB.) Second edition. Pp. 197; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

THIS excellent manual of gonorrhea in women was reviewed five years ago upon the appearance of the first edition. The present edition consists in the adding of a chapter on advances in technique, among which may be mentioned urethral dilatation and painting, the use of acriflavin in glycerin, suction, diathermy and amputation of the cervix. Vulvovaginitis in children is now treated by a paste of Bulgarian milk and castor sugar. P. W.

THE NERVOUS SYSTEM. By E. E. HEWER, D.Sc. (LOND.), and G. M. SANDES, M.B., B.S. (LOND), M.R.C.S., L.R.C.P. Pp. 104; 55 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$6.50.

MEDICAL students will be grateful for this volume. Clarity and brevity rule throughout and this treatment of a very complex subject has been achieved through the inclusion of many aptly chosen diagrams distributed throughout the text. The minute structure

and function of the component parts of the nervous system are given together but gross anatomy has been omitted.

Among other chapters included in Part I, are the neuron theory, changes following section of nerves; connections of the cerebellum, cranial nerves and basal ganglia; spinal fluid and autonomic system. Part II discusses sensory, motor, visual and cochlear pathways; cerebral cortex, reflex action, levels of integration and mechanism of coördinated muscular movement, together with other topics. Generally, pathology is not considered except hemi- and complete section of the cord, aphasia and nystagmus; but entire chapters are given to "results of interference" at many different levels. There is a comprehensive bibliography and a good index. N. Y.

THE NERVOUS CHILD. By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.). Fourth edition. Pp. 249; 8 illustrations. London: Oxford University Press, American Branch, 1929.

AN endorsement by the Bureau of Education of the Department of the Interior, Washington, D. C., together with the numerous and rapidly appearing editions and reprintings, speak emphatically of the usefulness of this little volume.

Designed primarily for mothers, on the care of preschool children, its actual realm extends well beyond that period, and may with profit be read by physicians, nurses and teachers.

Chapters range all the way from "Toys, Books and Amusements," to "The Underlying Disturbances of Metabolism in the Nervous Child." To really appreciate its merits—its many helpful and unusual suggestions—one must read the book. N. Y.

BOOKS RECEIVED.

NEW BOOKS.

*Chemistry for Nurses.** By IRENE KOECHIG, A.M. Pp. 304; 7 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$2.75.

Research and Medical Progress and Other Addresses. By J. SHELTON HORSLEY, M.D. Pp. 208; 6 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$2.00.

The addresses have to do largely with factors that make for medical progress and improvement in medicine, and do not deal with technical details of surgical procedures.

*Die Medizin der Gegenwart in Selbstdarstellungen.** Pp. 219. Leipzig: Felix Meiner, 1929. Price, 8.50 Mk.

* Reviews of titles followed by an asterisk will appear in a later number.

- Disease and the Man.** By GEORGE DRAPER, M.D. Pp. 270; 52 illustrations. New York: The Macmillan Company, 1930. Price, \$4.50.
- Tuberculosis in Public School Children.* By EUGENE L. OPIE, M.D. and collaborators. Pp. 636; 43 illustrations. Reprinted from The American Review, Vol. 20, No. 4, October, 1929.
- Surgery at the New York Hospital One Hundred Years Ago.* By EUGENE H. POOL and FRANK J. MCGOWAN. Pp. 188; 24 illustrations. New York: Paul B. Hoeber, Inc., 1929.
- The Medical Clinics of North America*, Vol. 13, No. 4 (Philadelphia Number) January, 1930. Pp. 301; 13 illustrations. Philadelphia: W. B. Saunders Company.
- Bibliotheca Osleriana.** A Catalogue of Books illustrating The History of Medicine and Science collected, arranged, and annotated by SIR WILLIAM OSLER, Bt. Pp. 785. Oxford: At the Clarendon Press, 1929.
- Roentgenographic Technique.** By DARMON ARTELLE RHINEHART, A.M., M.D. Pp. 388; 159 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$5.50.
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- Treatment in General Practice.** By HARRY BECKMAN, M.D. Pp. 899. Philadelphia: W. B. Saunders Company, 1930. Price, \$10.00.
- The Mechanism of the Larynx.** By V. E. NEGUS, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 528; 160 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$13.50.

NEW EDITIONS.

- Symptoms of Visceral Disease.* By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P. Pp. 426; 87 illustrations and 10 color plates. Fourth edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$7.50.
- Essentials of Medical Electricity.* By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), M.R.C.P. Pp. 443; 127 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1929. Price, \$4.25.
- Getting Well and Staying Well.* By JOHN POTTS, M.D. Pp. 221. Second edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.00.
- Bergey's Manual of Determinative Bacteriology.** By DAVID H. BERGEY. Pp. 589. Third edition. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.
- The Dietary of Health and Disease.** By GERTRUDE I. THOMAS. Pp. 276; 3 illustrations. Second edition. Philadelphia: Lea & Febiger, 1930. Price, \$2.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Tuberculosis of Insidious Onset and of Acute Onset: Necessity of Different Diagnostic Criteria.—Tuberculosis still holds the first rank as the cause of death during the most productive period of life, from fifteen to forty-five years of age, writes POTTENGER (*J. Am. Med. Assn.*, 1928, 93, 1801). For this reason the disease is of extreme importance to the medical man. It is a well-known dictum that the earlier the diagnosis is made the greater is the likelihood of the patient's recovering. For this reason it is of primary importance to recognize the signs of its early appearance. There are two types of onset—the acute and the insidious. The symptom complex of the latter development is familiar to most every one, whereas the more acute and abrupt onset of the disease is not recognized in many cases. The nature of tuberculous infection depends very largely upon the basis of the allergic response of the individual to the tubercle protein. Reviewing this particular phase of chronic tuberculosis, the author states that tuberculosis differs from most of the acute infectious diseases in that there remains after infection viable organisms in the body likely to cause a series of future reinoculations under certain circumstances. There is not produced a lasting immunity for this reason, and the disease develops because of a succession of reinfections with bacilli and bacillary protein. If the number of organisms is limited, the onset would be insidious. If, on the contrary, a large number of bacilli stimulate the immunologic reactions of the patient, there will be marked allergic phenomena. A toxic syndrome, with rapid pulse, increased temperature, malaise, loss of appetite and poor digestion, with cough, spasticity of the muscles of the shoulder girdle, lagging and bacilli in the sputum takes place. As far as the toxic group of symptoms is concerned, the condition cannot be differentiated

from any other acute infection, but the cough and expectoration should direct attention to the lungs. Repeated examinations of the sputum are therefore indicated. Bacilli will often be found in large numbers. This acute onset is very frequently followed by a period of quiescence during which the toxic symptoms may entirely disappear or may reappear again after a period of time. The patient is presumed to have an acute respiratory tract infection. It is to avoid the possibility of making such a mistake that numerous sputum examinations should be made, particularly if the patient gives a history of having had repeated colds.

SURGERY

UNDER THE CHARGE OF

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Bronchogenic Contamination in Embolic Abscess of the Lungs.—ALLEN, ADAMS and HIDINA (*Arch. Surg.*, 1929, 19, 1262) say that attention was called to the facts that abscess develops much more readily from embolic than from intrabronchial inoculation of the lung and that the lung appears to be in general much more resistant to necrosis and suppuration than are the other tissues. Experimental test was made of the hypothesis. The greater vitality of the lung in pyogenic infections is due mainly to a greater blood supply and the elimination of the pulmonary circulation as by embolism reduces the blood supply and tissue vitality to that common level. It was concluded that the hypothesis is essentially correct. This principle was applied to explain the pathogenesis of certain suppurative diseases of the lungs, viz.: postoperative abscess of the lung, especially following sterile operations; postpneumonic abscess of the lung, especially following sterile operations; postpneumonic abscess of the lung and empyema and relapses in suppurative diseases of the lung in general. Hemorrhagic infarct may have a similar origin.

Fifteen Years Devoted to the Use of Radium in Neoplastic Diseases.—QUIGLEY (*Urol. and Cutan. Rev.*, 1929, 33, 800) says that radium has established a definite place in modern medicine. Its field of usefulness is constantly increasing, not only by extensions in the fields in which it has been established, but also in new fields, such as the treatment of exophthalmic goiter and tubercular glands. While the bulk of the radium work is with cancer, radium also has a very wide field of usefulness in benign conditions. Local and accessible cancer should be treated by choice with radium. Cases involving considerable bulk should be treated by means of a combination of preoperative radiations with radium, surgical operation and postoperative radiation. Certain clinical facts concerning cancer growing in certain body locations are fundamental, and these facts must be taken into consideration if we are

to use radiation to the best advantage. Judgment in estimating radium dosage is a thing that can be learned only by long experience. The author knows of no way for physicians or students to acquire skill in the use of radium except by working with someone already skilled in its use.

Surgical Aspects of Undulant Fever.—SUPSU and BOWERS (*Am. J. Surg.*, 1929, 7, 597) state that undulant fever has rapidly become a most important public health problem. Over 1000 cases have been discovered in this country in the last few years. Undulant fever possesses important surgical aspects, chiefly because of the ease with which it may be confused with appendicitis and cholecystitis in certain cases. In view of the predilection of the organism for the genital tract it bears an etiologic relationship to certain cases of abortion, tubo-ovarian abscess, seminal vesiculitis, prostatitis, epididymitis and orchitis. The joint manifestations of the disease make it a diagnostic problem for the orthopedic surgeon. Contrary to the frequently expressed belief that undulant fever is difficult to recognize clinically, the clinical manifestations of the disease were sufficiently characteristic to enable physicians to make an initial diagnosis of undulant fever in over one-third of the cases reported here. The relationship between the consumption of raw milk from cattle infected with the organism of contagious abortion (*Brucella abortus*) and the occurrence of undulant fever in human beings has been established.

The Effects of Hypertonic Dextrose Solution Upon Experimental Diffuse Peritonitis.—BUCHINDER, HEILMAN and FOSTER (*Surg., Gynec. and Obst.*, 1929, 49, 788) claim that rapidity of absorption in the largest measure governs the prognosis of acute, diffuse peritonitis. Fibrin is the most important factor in controlling the rate of absorption. Fibrin is diminished or absent in the more virulent cases because of dilution of the exudate. The streptococcus is most commonly identified with this abundant exudate and the accompanying virulent course of the disease. The addition to such an inflammatory exudate of a transudate produced by the intraperitoneal injection of hypertonic dextrose solution produces a more rapid spread of the infection and insures lethal outcome. It seems probable that an abundance of thin exudate serves to prevent ileus by mechanical isolation of intestinal loops. The results of this experimental study do not agree with the published reports of the similar treatment of peritonitis in man.

Tuberculosis of Colon Simulating Cancer.—BARGEN, COPELAND and RANKIN (*Ann. Surg.*, 1930, 91, 79) say that tuberculous lesions of the colon, as a primary disease, have been reported. When they occur their common site is the ileocecal region. Tuberculosis of the sigmoid colon is one of the rare forms of tuberculosis of the colon. The absence or scantiness of the bleeding in the presence of a large obstructive lesion argues against the presence of malignant conditions. Rankin and Yeomans previously have noted the similarity of the roentgenographic defects produced by tuberculous and malignant lesions. The absence

of tuberculous lesions elsewhere than in the sigmoid colon is noteworthy. Pincoffs and Boggs noted that in tuberculosis of intraabdominal origin, masses of tuberculous nodules will occur in various places and that there is more matting of viscera than with tuberculosis of distant origin. The absence of lesions in the rectum and in the rectosigmoid portion of the colon, as noted by proctoscopic examination, argues against the presence of an ulcerative type of lesion and further, the absence of deformity or of any defect of the colon elsewhere is evidence against the presence of tuberculosis of the proximal portion of the colon and in favor of the disease being of the hyperplastic type.

Evaluation of Cardiac and Circulatory Stimulants for Surgical Patients.—PHELPS (*Ann. Surg.*, 1930, 91, 24) states that epinephrin increases the cardiac output for a brief period (less than seven minutes) with a tendency in many instances to return to a point below the original output. Caffein actually diminishes the cardiac output. Camphorin-oil depresses the cardiac musculature and dilates the coronary vessels. Ephedrin stimulates the accelerator mechanism—large doses depress the heart muscle and cause a fall in blood pressure. Pituitrin constricts the vessels in general, but dilates the heart to a very high degree, immediately after its administration. Strychnin has no tonic effect on the heart. The use of insulin in shock is harmful. Digitalis, in adequate dosage, is a cardiac tonic and a general vasoconstrictor, the action of which is dependable, pronounced and sustained.

The Serology of Syphilis.—KAHN (*Urol. and Cutan. Rev.*, 1930, 341, 1) noted that five requirements for optimum precipitation are observed in syphilis; optimum concentration of antigenic lipoids in the antigen, proper physical state of antigen suspension, correct quantitative relation between serum and antigen suspension, shaking—as a probable aid in hastening collision between the interacting particles while total dilution of a suspension-serum mixture should be a minimum. The Sach school believes that serum reactions in syphilis fall under immunity reactions. The Landsteiner school believes that there is not sufficient experimental evidence for this view. This brings us to the practical application of serum reactions in syphilis. A positive reaction in a case for diagnosis is generally accepted to mean active syphilis and to indicate therapy. The significance of a positive reaction after intensive therapy, however, is still a matter of opinion among different workers. Some, especially Wile, have for a long time contended that a positive serologic reaction may be an expression of immunity in syphilis to the same degree that a positive Widal reaction may be an expression of immunity in typhoid. Thus there is difference of opinion today as to the significance of positive serologic reaction in relation to syphilis therapy. Further experimental evidence is necessary before the immunological character of these reactions will be fully established. In addition, it is hoped that the laboratory will develop some biologic criteria for cure in syphilis.

THERAPEUTICS

UNDER THE CHARGE OF

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The Use of Levulose With and Without Insulin in the Control of Severe Diabetic Acidosis.—On the basis of carefully controlled investigations, PUCSKO (*München. med. Wchnschr.*, 1929, 76, 1755) recommends the intravenous injection of levulose in doses up to 10 gm. in 50 per cent solution combined with the administration of 20 units of insulin intravenously or from 20 to 40 units subcutaneously, for the effective control of ketosis in refractory cases of severe diabetes. In contrast to the very rapid effects of a similar combination of dextrose intravenously and insulin, the levulose insulin combination acts rather slowly, but its action seems to increase with repeated administrations. For immediate control, therefore, an initial administration of the glucose-insulin combination may be advisable, but thereafter the combination with levulose proves effective. After the control of ketosis has been well established, the oral administration of levulose combined with injection of insulin in the customary doses maintains control in a most satisfactory manner and has the advantage over glucose that the treatment can be carried out satisfactorily on ambulatory patients.

The Treatment of Influenza with Para-benzoyl-para-amino-benzoyl-amino naphthol 3 to 6 sodium sulphonate (S.U.P., 36).—During the influenza epidemic of the present year every alternate case in which the disease had not existed over forty-eight hours was treated by PEARCE (*Brit. Med. J.*, 1929, 663) with intramuscularly administered S.U.P., 36. The initial dose was 0.5 c.cm. (representing 0.005 gm.) as a rule, occasionally 0.75 c.cm. If the patient did not recover, a second dose of 0.75 cc. was given on the fourth day following the initial dose. Half the injected patients also received 2 to 5 grains of calomel. A comparison of the average duration of pyrexia, headache, muscular pain, the number of days in bed and the number of days loss of work was distinctly in the favor of the patients treated with S.U.P. 36. The earlier the injection, the greater the benefit derived, according to the author's claim.

Sanocrysin Treatment of Pulmonary Tuberculosis.—According to CLARKE (*Brit. Med. J.*, 1929, p. 576) it is safe to start the sanocrysin treatment of pulmonary tuberculosis with a dose of 0.25 gm. This amount is gradually increased at weekly intervals to 0.75 gm. or to

1 gm. in heavier patients. These larger doses are repeated four or five times at ten-day or fortnightly intervals. Some patients do not tolerate even small doses, and the treatment has to be abandoned. Diarrhea, vomiting, dermatitis, stomatitis, neuritis, albuminuria, febrile reactions and loss of weight are the complications observed. Cachexia, intestinal tuberculosis and disease of the kidneys are contraindications. The most beneficial response was observed in the fibroid type of phthisis—55 per cent of the patients were discharged without tubercle bacilli. In the exudative type of phthisis, with the exception of the early cases; sanocrysin is less beneficial. The beneficial effect manifests itself in the disappearance of the tubercle bacilli from the sputum. The heavy cottony shadows of the Roentgen ray picture may be replaced by well-defined markings. Contraction of the lung may also develop. The moist crepitation may clear up, being replaced by diminished breath sounds. If the disease is entirely unilateral, collapse therapy is preferable and sanocrysin should not be applied. If, in addition to the widespread involvement of one side, there is some involvement of the better lung, combined sanocrysin and collapse therapy is indicated. Sanocrysin is not a cure for tuberculosis of the lungs, but it is a valuable aid to treatment if used with caution and discrimination.

Experimental Studies on Analgesics.—Directing attention to the unsatisfactory basis of our present evaluation of analgesic drugs (HAFNER (*Deutsch. med. Wchnschr.*, 1929, 18, 731), discusses a method of accurately determining the analgetic dose of a variety of drugs on mice or rats. Employing this method he finds that the following substances are without analgetic action after systemic administration of the largest possible doses: thebain, apomorphin, scopolamin, coniin, veratrin, aconitin, emetin, yohimbin, camphor, cardizaol and coramin. No definite analgetic action is produced by caffein, quinin, salicylic acid, aspirin, antipirin, tropacocain, sodium bromide and a few others. Mescaline, cocain and many of its substitutes produce a mild analgesia. Those agents which are effective analgesics comprise opium and its preparations, morphin, codein, dionin, papaverin, narcotin, heroin and analogous derivatives of codein or morphin; as well as atophanyl, phenacetin and particularly pyramidon. Comparative studies show that heroin is the most potent preparation for producing analgesia, being twice as active as morphin and only slightly less active than the new preparations, dilaudid and eucodal. Codein has one-third the activity of pantopon or of opium and the relationship between the activity of codein and pyramidon is approximately 1 to 3. Combinations of these several preparations in general show no synergism but merely demonstrate additive effects. On the other hand pyramidon combined with codein or other of the analgetic opium alkaloids produces marked potentiation. Thus one-eighth of the analgetic dose of codein plus one-half the corresponding dose of pyramidon produces complete analgesia. The same effect is obtained from one-third dose of codein plus one-fourth that of pyramidon. This combination, with or without the addition of narcotin, gives analgesia essentially equivalent to that produced by morphin, and is free from the undesirable effects of the latter alkaloid. An effective combination for man is a mixture of 25 mg. each of codein and narcotin with 200 mg. of pyramidon. It is

interesting to note that the various anesthetic and hypnotic preparations, including ether, chloroform, the alcohols and the derivatives of diethylbarbituric acid, and so forth, as well as magnesium sulphate, are virtually without analgesic action except in quantities which produce marked narcosis.

Exceptional Injuries to the Circulation by Insulin.—After reviewing many reported instances of circulatory disturbance caused by insulin, REINWEIN (*Deutsch. med. Wchnschr.*, 1929, 55, 951), reports in detail on two patients in whom the administration of insulin precipitated extreme degrees of congestive heart failure with all of its associated symptoms, including intense dyspnea, orthopnea and the development of general anasarca. In both the dyspnea was mistaken for the premonitory signs of diabetic coma and increasing doses of insulin were administered with the result that the cardiac failure was further aggravated. Both patients were relieved by the complete withdrawal of insulin, the introduction of virtual starvation, the restriction of fluid intake and the administration of strophanthin, digitalis and other circulatory stimulants. In one the diabetes was subsequently found to be very mild and controllable by diet alone. In the other it was marked and, after restoration of cardiac efficiency, small doses of insulin were necessary. So long, however, as the dose was kept small, no further difficulty with the circulation was encountered. The author points out that the experiences in these two patients further establish the necessity of proceeding cautiously with the administration of insulin in diabetic patients who manifest evidences of organic disease of the heart or circulation.

PEDIATRICS

UNDER THE CHARGE OF

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Vaccination of Children Against Typhoid and Paratyphoid.—HESSE (*Arch. de med. des enf.*, 1929, 32, 729) points out that nowadays the occurrence of typhoid and paratyphoid is limited principally to women and children. He attempts to explain this by the fact that in military service vaccination against these diseases is compulsory. From a review of the literature and his personal experience he feels that it is absolutely necessary to vaccinate by subcutaneous inoculation all children older than three years of age who live in an environment where the danger of contagion is great. Antidiphtheritic vaccination may be performed at the same time. With the typhoid and paratyphoid vaccination, protection is afforded for a period of only two years, after which revaccination may be done by subcutaneous injection or by taking the vaccine of Lumiere or Besredka. The contraindica-

tions to this procedure are tuberculosis or a weakened general condition and it should not be done in children with an acute infectious disease or in those having symptoms of cardiac or renal insufficiency or liver disorders.

The Pineal Form of Pubertas Precox.—BERBLINGER (*Deutsch. med. Wchnschr.*, 1929, 55, 1956) describes several forms of precocious puberty. The first type in which either hyperplasia of the suprarenal cortex or hypernephroma is found is more frequent in girls. The second is the genital form which is found in both sexes. In this type there exists other tumors or hypertrophy of the generative glands. The third type is the pineal form. Nearly all the cases so far reported were in boys. It was found that the pathologic changes occurring in this form of precocious puberty differ widely. Some cases were observed in which the pineal body itself was not affected but in which a tumor was found in the third ventricle. It is assumed that the pineal body and the nerve centers in this region are closely interrelated, but he also assumes that there are probably two forms of cerebral precocious puberty which he groups as the pineal type and the diencephalic type. The author further points out that in adult men with glioma of the pineal body hypertrophy of the testes has been observed. From this it would seem that the pineal body exerts an influence on the sex organs even after the age of puberty.

Chest Roentgenograms of Nontuberculous Children Suspected of Having Tuberculosis.—WOLFF and STONE (*J. Am. Med. Assn.*, 1930, 94, 458) found that the average number of previous diseases per case varied only from 2.2 to 2.6 for the various groups, with the whole series at 2.3. The average number of symptoms presented by each group varied between 1.4 and 1.8 per case. The average age of the whole series was eight years, the youngest patient being two years of age and the eldest fifteen years. It is of special interest that the group without increased markings in the upper lobes are a higher incidence of past respiratory diseases, especially bronchitis, measles and pneumonia, than in the group with increased markings. In one group with an incidence of previous diseases of 1.7 per child, with an average age of 3.5 years, showed in comparison with the clinic group a higher percentage of multiple axial vessels at the hili, a slightly higher percentage of multiple axial vessels up to 2 mm. in diameter in the upper left part of the chest, in vessels of 3 mm. in either lung field and a somewhat lower percentage of localized increase in the lung markings. There was no increase in the number showing positive d'Espine's sign, vertebral dullness, paravertebral dullness and dullness of the manubrium in the cases presenting multiple axial vessels at the hili. The definite impression gained by a survey of the entire study is that there are no marked variations in any of the groups. In roentgenograms of the chest in the children without acute illness and with negative tuberculin reactions may show single or multiple, large or small axial vessels in the hili, multiple axial vessels up to 2 or 3 mm. in diameter in the lung tissue, localized increased lung markings, localized plural thickenings or none of these shadows. From this it is apparent that a diagnosis of tuberculosis of the mediastinal glands or of lung tissue cannot be based on the findings of the

roentgenograms. In this study no calcifications, glandular tumors or localized pulmonary infiltrations were found and no definite correlation was found to exist between positive roentgenogram findings and the clinical history.

The Effect of Large Amounts of Milk Sugar on the Stools and Nutrition of Infants.—BARENBERG and ABRAMSON (*Arch. Pediat.*, 1930, 47, 1) made a study over a period of more than a year, including both summer and winter months, in order to determine the effects of large quantities of milk sugar on the frequency and the character of the stools of infants. They desire to determine whether milk sugar acted as an intestinal irritant and whether it had a laxative effect in infants when fed even in very high concentrations. The first part of their investigation which was conducted during the summer months showed that ingestion of even 12 to 15 per cent by weight of milk sugar did not bring about loose stools. The second part of the investigation was conducted from January to June. Comparison made with a control group of infants showed that the diarrhea which followed in some was due primarily to the milk sugar, but was secondary to a nutritional disturbance in which infection played the chief part. Sugar was not found in the urine or in the stools either in conditions of health or of disease in spite of the fact that the babies received approximately 15 to 17 gm. of milk sugar per kilogram of body weight. Repeated microscopic examinations of the stools showed that a Gram-negative type of flora predominated at all times and that few Gram-positive, acidophilic organisms were noted. The infants receiving large amounts of milk sugar responded with a better rate of growth than did the control group. Milk sugar is a safe carbohydrate for the modification of cows' milk and does not have a laxative effect in infants when used even in high concentration.

The Relative Digestibility of Unsweetened Evaporated Milk, Boiled Milk and Raw Milk by Trypsin in Vitro.—WALLEN-LAWRENCE and KOCH (*Am. J. Dis. Child.*, 1930, 39, 18) observed that raw milk when pasteurized, boiled or evaporated undergoes changes which make it more readily digested by trypsin *in vitro* than raw milk. The changes are proportionally greater in boiled and evaporated milk than in pasteurized milk. The increase in trypsin digestibility appeared to be a function of a temperature to which the milk is heated and the length of time for which it is heated. The increase in trypsin digestibility is not correlated with the changes in the buffer system of milk incidental to heating nor is it correlated with any changes in the casein of the milk. The change in trypsin digestibility is due to some heat-labile constituent of the whey. It is thought that this inhibitory substance will be found in the albumin portion of the whey and calcium and phosphate are probably not involved. It has been assumed that the tryptic inhibitor reacts with trypsin to inactivate it, and on this assumption therapeutical curves have been calculated which show a marked resemblance to the curves obtained by actual experiment. The authors feel that no practical significance can be attached to these results until the effect of pepsin digestion as a precursor to tryptic digestion has been studied.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Industrial Dermatoses: Their Causation, Recognition, Prevention, Treatment.—SIBYL OVERTON (*Brit. J. Derm. and Syph.*, 1929, 41, 255) stresses the recent prominence of skin affections among industrial disabilities in England. In 1927 more certificates of disability were issued for dermatoses than for any other compensatable condition. Important among the causes of serious cutaneous disabilities are chrome, pitch, tar and alkalies. The latter have held first place as causative factors for the past three years. Other important causes have been degreasing agents such as turpentine and petrol; sugar and dough are also responsible for an increasing number of cases. Important secondary factors are: (1) Minute particles of filings in machine shops mixed with oil and causing microscopic injuries; (2) infection; (3) absence of cleanliness of person and clothing in the sebaceously active male adolescent. Second attacks of dermatitis are common, while factors of sensitization develop as in ordinary cases of dermatitis. An inquiry into certain dyeing and polishing industries has determined that the methods of removal of dyes and chemicals from the hands have been the inciting cause of the ensuing dermatitis. Prevention is necessarily linked closely with causation. "Remove the Cause" does not sum up all preventive measures for dermal irritants must be handled. The problem is to handle them with safety. The author stresses three main preventive procedures: (1) Emollients before and after work, providing both protection and a means of later easy removal of the irritant; (2) complete removal of the irritants by harmless methods several times each working period; (3) frequent inspection by experienced observers to enforce early treatment of minor injuries and burns, scrupulous cleanliness of hands and overalls and removal from irritants with prompt treatment for early cases. Under the same title, DYSON (*ibid.*, p. 264) emphasizes certain common characteristics in the recognition of industrial dermatoses, that is, the occurrence of the inflammation first at the exposed site and the occurrence of a refractory period of sensitization after the subsidence of the acute inflammation recognized by a vasomotor disturbance and significant of the possibility of an early relapse. A liability to relapse reflects a general sensitization comparable to an "anaphylactic state." The general sensitization from prolonged or repeated attacks causes the patient to react to the external irritant on any portion of the skin. Seborrhea and secondary pyogenic infections

appear to favor the appearance of the sensitization phenomena. Predisposition to a trade dermatitis is similar to those of ordinary eczema, that is, hyperidrosis and ichthyosis. The author found a high blood sugar present in cases with intense pruritus, but an inflammatory or discharging surface was accompanied by a slight decrease in blood sugar. Treatment of sensitization cases was effected by the intramuscular injection of the patients' whole blood. The prognosis depends on the duration and the number of previous attacks. With a local or general sensitization the prognosis is less favorable and a relapse becomes almost certain. Treatment in the main means protection from irritants, including soap and water, protection from weather and sudden changes in temperature. Lotions seem to work best in the hyperidrotic patient, while an ointment is indicated for the ichthyotic. Roentgen ray and silver nitrate have proved additional aids in the sensitization cases. Preventive measures should include: (1) Examination before engagement of the employee; (2) periodic medical examinations during employment; (3) the avoidance of the indiscriminate use of emollients as a prophylactic measure, inasmuch as the hyperidrotic workman will be unnecessarily harmed.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Prognostic Value of Histologic Findings in Cervical Cancer.—Much work has been done in recent years in an effort to correlate the histologic findings in cases of cervical cancer with the prognosis, and in most instances the investigators seem to be of the opinion that the microscopic picture is of great value. In other words, when the removed specimen shows a histologic picture representative of a high degree of malignancy, the prognosis is relatively poor and *vice versa*. A dissenting opinion has been presented by THIBAudeau and BURKE (*J. Cancer Research*, 1929, 13, 260), which is based upon the results obtained by radiation therapy in cancer of the cervix. In their work they used the classification of Broders, namely: Group 1: Tumors in which 75 to 50 per cent of the cells show differentiation with 25 to 50 per cent of undifferentiated cells. Group 2: Tumors in which 50 to 25 per cent of the cells show differentiation with 50 to 75 per cent of undifferentiated cells. Group 3: Tumors in which 25 per cent or less of the cells show differentiation with 75 to 100 per cent of undifferentiated cells. In their series they found that the histologic grouping and

malignancy indices are of limited value in the prognosis in cases of epithelioma of the cervix. As evidence of this they state that in a series of 28 cases of epithelioma of the cervix in which no recurrence was noted for five or more years following irradiation 25 per cent of the cases belonged to Group 3, 50 per cent to Group 2 and 25 per cent to Group 1.

Vaginal Administration of Follicular Hormone.—In a preliminary note on their experimental work POWERS, VARLEY and MORRELL (*Endocrinology*, 1929, 13 395) state that they prepared the estrus-inducing hormone of the ovary in the form of a gelatin pessary for vaginal administration. The check of the gelatin pessaries by injection of a watery emulsion of them into white rats showed that no loss in potency occurred in their preparation. They have been able to induce the estrus cycle in spayed albino rats by the vaginal administration of the hormone. The ratio between the pessary dose and the subcutaneous dose is probably about 3 to 1. Menstruation has been induced in spayed monkeys by the vaginal administration of these pessaries, using as low as 150 units. This work would seem to show that satisfactory absorption occurs from the vagina so that this method of administration may be used as a more pleasant manner of administration than the usual and sometimes painful method of subcutaneous injection.

Irradiation of Cancer of the Cervix.—A review of the literature reveals a regrettable diversity of opinion on the radiologic management of cancer of the uterine cervix states LAWRENCE (*Radiology*, 1929, 12, 429) as he pleads for a standardization in the methods of treatment. He believes that it can be theoretically demonstrated and upheld by recorded results that the gamma rays of radium and Roentgen rays are equally important in the radiotherapeutic management of carcinoma of the cervix and that no one is justified in using one to the exclusion of the other. In early cases radium is of chief importance, but all of these cases would be safer if external radiation were added shortly after radium treatment. In borderline cases radium and Roentgen ray are of equal importance. Either may precede, but the other should follow within a week or ten days as a supplement. In advanced cases the Roentgen ray is of far greater importance than radium and should always be given first. Its action, however, should be supplemented by guarded doses of radium from within as there are no contraindications to such supplementary treatment. Although individual variations in technique are to be expected, the author believes that the profession should be able to agree upon the principles underlying the management of each of the three degrees of this disease.

Nasal Administration of Sexual Hormones.—PRATT and SMALTZER (*Endocrinology*, 1929, 13, 320), of the Henry Ford Hospital, are quite enthusiastic about the nasal-spray method of administering hormones of the ovary and pituitary gland, since by this method the patient controls the administration and is not obliged to visit the doctor for hypodermic injections. They found that when the hormone has been sprayed into the nose, all of the material appears to be absorbed and there has been no sign nor symptom of local irritation. The method

of administration is so simple that the patients have no difficulty in managing it at home. While there has been no complaint following the use of the plain hormone, some patients prefer a specially scented preparation. When coryza or other local abnormality contraindicates the application to the nasal mucosa, the vaginal mucosa may be used. Frequently repeated doses can be administered by the patient approximating normal conditions in a way that cannot easily be accomplished by hypodermic injections, so that this method increases the field of usefulness of the hormones. They have applied the method to the use of ovarian hormone, pituitrin, pitresin and pitocin and find that it is efficient, easy and safe.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Pronounced Short-sightedness and the Interruption of Pregnancy.—BIRCH-HIRSCHFELD (*Ztschr. f. Augenh.*, 1929, 68, 127) reports 3 cases in which myopic women suffered reduction in visual acuity and increasing short-sightedness during pregnancy. In all 3 cases the following pregnancy was interrupted since another, similar advance in the trouble would leave the patients blind or nearly so. While all myopic women do not suffer such a change, he concludes that high-grade myopia of both eyes with advanced central changes in the retina and choroid and pronounced poor sight in one eye with similar, though less marked changes in the other eye justify therapeutic abortion. Particularly is there danger of blindness or poor vision approximating it, due to hemorrhage and vascular obliteration in the better eye if there was a decrease of visual acuity with or without advance in the myopia during the earlier pregnancy.

The Possibility of Influencing Glaucoma by Roentgen Irradiation of the Thyroid.—The significance of increased tonus of the sympathetic in glaucomatous eyes has been suspected by earlier authors. Krasso (*Ztschr. f. Augenh.*, 1929, 68, 163) investigated 31 patients to determine the relations of basal metabolism and thyroid hyperfunction respectively, and sympathetic tonus in the vascular region of the eye to glaucoma. Five of these were treated with Roentgen rays to determine whether in certain cases a latent hyperthyroidism might be in causal relation to the increase in ocular pressure or whether it had a parallel course, since Roentgen ray treatment of the thyroid can reduce the basal metabolism and make symptoms of hyperthyroidism disappear. In all 5 there was a decrease of the general troubles belonging to the symptom complex of latent hyperthyreosis. In only 2 cases was there a long, continued decrease in the ocular pressure together with change in the visual fields and in central vision. In both of these the only

symptoms indicating glaucoma were the appearance of glaucomatous excavation and increase in pressure up to 30 mm. Hg as well as decrease in visual acuity and change in the visual fields. In the 3 other cases the pressure was above 30 mm. Hg and there were also attacks of clouded vision. It would appear that it is possible to find cases of chronic glaucoma in which there is a connection between hyperfunction of the thyroid and vasomotor disturbances on the one hand and glaucoma on the other. The fact that glaucoma is a disease of advanced age while disturbances of the vasomotors and hyperfunction of the thyroid appears in all ages, favors the assumption that here the predominance of the thyroid is due to underfunction of the sexual glands. Borak has found that this hyperfunction of the thyroid during the climacteric is very favorably influenced by Roentgen irradiation. It is impossible to say as yet just what cases of glaucoma will respond to Roentgen irradiation of the thyroid. Basal metabolism is not a determining factor. Neither can the permanence of the change be discussed since the cases here reported have been observed for only five months.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Acute Infectious Mononucleosis from the Point of View of an Otolaryngologist.—Although comparatively rare, acute infectious mononucleosis, since first described by Spruant and Evans as a clinical entity, has held forth much in the way of academic and practical interest to the otolaryngologist. As its name indicates one of the outstanding features is a marked increase in the mononuclear cells of the blood; the other preponderating finding consists of enlarged cervical lymph nodes. This characteristic has led to the analogy between “glandular fever” and acute infectious mononucleosis, although there is no proof that they are identical. In describing three cases as acute infectious mononucleosis, LA MOTTE (*Arch. Otolaryngol.*, 1929, 10, 171) calls attention to the wide latitude in appearance of the pharynges of these patients, varying from virtually normal looking throats to acutely inflamed tonsils or postpharyngeal lymphoid nodules, or even to exudative and ulcerative lesions of tonsils, tonsil stumps, or pharyngeal wall. The causative agent is unknown. The prognosis is good. The lymph nodes rarely, if ever, suppurate. In concluding, the author suggests that “it may be that through the otolaryngologist more cases will be recognized and a deeper study will be made than in the cases here reported, thus contributing, perhaps, to the sum total, of knowledge of this interesting disease.”

Trigeminal Disturbances of Otitic Origin.—Long have otolaryngologists been concerned about the transmission of impulses of pain to the ear from the sphenopalatine region and other parts of the trigeminal distribution, as well as from those originating in the domains of the facial, glossopharyngeal and vagus nerves. Conversely, equal significance has not been given to the reflection of pain from the aural apparatus to the areas supplied by these cranial nerves. While it has been observed not uncommonly that *acute* inflammatory processes of the middle ear and mastoid are capable of producing pain about the face, the same possibility has not been accorded to the *chronic* forms of otitis media and mastoiditis. With this in mind, HANSEL (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 335) presented the data of 3 cases to demonstrate that pain can be referred to the second and third divisions of the trigeminal nerve as a result of chronic suppuration of the tympanic cavity and mastoidal cells. After reviewing the embryology, anatomy and neurohistology of the subject, he states that "in the final analysis of the nerve supply of the middle ear, mastoid and contiguous cutaneous area, it is apparent that there are intimate anastomoses between the various nerves involved to such an extent that they all form a nerve plexus." Moreover, several pathways along which these impulses may travel from the otitic structures to the "trigeminal areas" are indicated and their importance evaluated.

Pemphigus Primary in the Larynx.—Pemphigus involving the pharyngeal and oral mucosa primarily or secondarily to its manifestation on the skin is not infrequently seen. Pemphigus restricted to the larynx as a primary lesion for a period of twelve weeks before cutaneous involvement is of most unusual occurrence—even when considering *obscure* laryngeal conditions. In reporting a seemingly clear-cut case of pemphigus presenting early blebs on the epiglottis and right arytenoid, MURPHY (*Arch. Otolaryngol.*, 1929, 10, 188) by way of differential diagnosis, points out that the laryngeal lesions produce hyperemic spots resembling a superficial angioma in contradistinction to the diphtheroid patches produced by maceration of the denuded areas in the mouth. Inasmuch as the blebs may form and rupture in a few hours, repeated daily examinations should be made in all suspected cases.

Value of Barbitol Before Local Anesthesia.—The most efficient agent to effect anesthesia of mucous membranes by topical application is cocain—an admittedly dangerous drug because of its highly poisonous potentialities: In view of the fact that a suitable substitute for cocain—one capable of producing satisfactory anesthesia and at the same time of exerting no untoward systemic effects—is as yet unknown, the rhinolaryngologist has been forced to continue its employment in various operative procedures of the nose and throat. In the absence of an ideal local anesthetic, intensive investigation has been undertaken in the hope of finding some substance which could act as a more successful prophylactic or antidote to that distressing and not infrequently fatal condition—acute cocainism—than such ordinarily used drugs as morphin, atropin and scopolamin. As previously indicated in these columns,¹

¹ Phenobarbital in the Prophylaxis and Treatment of Acute Cocain Intoxications, *Am. J. Med. Sci.*, 1927, 173, 441.

experimental and clinical evidence has pointed to the various salts of barbituric as the most promising preparations whereby the toxic action of cocain, and to a lesser degree novocain and others, might be obviated or neutralized. Of these, the popular compounds have been diethyl barbituric acid (barbital) and its sodium salt (sodium barbital), phenyl ethyl barbituric acid (luminal) and n-butyl ethyl barbituric acid (neonal). Interested in this important problem, BARLOW (*Ann. Otol., Rhinol and Laryngol.*, 1929, 38, 421) reports encouraging clinical results following the oral administration of 5 or 10 grains of sodium barbital or of 1½ grains of neonal, one hour before operation.

RADIOLOGY

UNDER THE CHARGE OF

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Late Effects of Treatment of the Thymus.—A study by BARNES (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 220) of 63 children who received irradiation treatment of the thymus from three and a half to eight years ago fails to demonstrate any constant deviation from normal, in either the physical or mental spheres, which might be attributed to the treatment, although relatively high dosages were used.

Etiology of the Ill-health of Children Born After Irradiation.—This study represents part of an investigation by MURPHY and GOLDSTEIN (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 207) in the Institute of Gynecologic Research, University of Pennsylvania. Twenty-four per cent of 650 pregnancies associated with pelvic radium or Roentgen irradiation (preconception or postconception in time) ended in abortion; 13 per cent terminated in the birth of unhealthy children. One out of every 10 or 11 children born after *preconception* pelvic irradiation was unhealthy, whereas one out of every 2 children born after *postconception* irradiation was unhealthy. The ill-health of 24 of the 46 unhealthy children born after *preconception* irradiation was attributed to such influence as the following: (a) Six cases of child health disturbances were found to be due to maternal ill-health prior to irradiation or during pregnancy. (b) The ill-health of 13 children was believed to have been the result of complications incident to delivery or of prematurity. (c) In 3 cases the ill-health was believed to be the result of accidental causes. (d) Two unhealthy children later became healthy. The etiology of the ill-health of 22 children could not be determined. In this group there were only 7 seriously defective children. Only one child out of every

59 children born after *preconception* irradiation exhibited some gross anatomic defect of unknown origin. In this small number (one in 59) of defective children the disturbance may have been caused by the previous ovarian irradiation, but it is the belief of the writers that if the irradiation had been the etiologic factor in the production of the condition, the defects would have occurred with greater frequency, regularity, and uniformity. Finally, it cannot be stated with certainty that preconception maternal pelvic irradiation is entirely free from danger to subsequent offspring because of the occurrence of a few defective children born after such treatment.

Radiotherapy for Tumors of the Testis.—DESJARDINS, SQUIRE and MORTON (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 137) state that Ewing divides testicular tumors into three groups: (1) the relatively benign and slow-growing teratomas composed of highly differentiated tissues arranged to suggest adult organs; (2) an intermediate group including the less differentiated, or teratoid, tumors, and (3) the most common and most malignant tumor of the testis, often miscalled sarcoma, but which he designates as embryonal carcinoma. Of 101 tumors studied by Desjardins and his associates, 69 were embryonal carcinomas (seminomas of Chevassu); 27 were mixed, or teratoid, tumors; 2 were teratomas or testicular dermoids; 2 were sarcomas and 1 had features suggesting chorioma. A comparison of surgery and radiotherapy cannot be made because they are used in different groups of patients. Radiotherapy is employed only after surgery has exhausted its efforts, or when, because the disease is too extensive, surgery cannot be employed. All that can be said for the present is that, in a small number of cases surgical removal of the tumor results in permanent cure; that radiotherapy is a valuable method of treating inoperable cases or cases in which metastasis has occurred in spite of operation, and that the most common tumor of the testis, embryonal carcinoma, is peculiarly and characteristically vulnerable to irradiation, thus providing a means of differentiating such tumors from other newgrowths. The results in embryonal carcinoma are always better and more lasting than in the mixed, or teratoid, tumors. Roentgen or radium rays have little if any influence on true testicular teratoma.

Bronchiectasis.—In about 60 per cent of all cases a diagnosis of bronchiectasis can be made from a study of the plain films, according to HARTUNG (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 120). Abnormalities of the bronchial wall plus a variable amount of air and secretion in the dilated bronchi produce the Roentgen image associated with bronchiectasis. It is characterized by an increase of the linear markings with small irregular densities, usually occurring in the lower lobes. In the advanced uncomplicated case there is a honeycomb appearance which is almost pathognomonic. In the majority of the remaining 40 per cent the plain films will reveal findings of a nature to indicate the probable presence of bronchiectasis or the desirability of further investigation by bronchography. Diagnostic bronchography with iodized oil is absolutely essential for obtaining accurate information relative to the nature, situation and extent of bronchiectasis.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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New Vestibular Complexes for Localization of Lesions of the Brain.—

FISHER and GLASER (*Arch. Neur. and Psychiat.*, 1929, 21, 876) present a study of vestibular reactions in 139 cases of brain lesions. They consider that while well-developed spontaneous nystagmus in any direction indicates a pathological condition, only vertical nystagmus is specifically indicative of a pathologic condition of the brain as it does not occur in peripheral lesions. Poor pelvic girdle movements are also suggestive of a brain lesion and there is a disproportion between nystagmus and vertigo after turning. Disproportion in the activity or duration of the responses from the horizontal and vertical canals of the same side after douching, or loss of nystagmus from the vertical canals with past pointing, perverted nystagmus, perversion of direction after stimulation, dissociated movements of the two eyes after stimulation, a loss of all vestibular responses after stimulation with good hearing, and conjugate deviation of the eyes after stimulation instead of the full nystagmus are all suggestive evidence. In all cases presented one or more of the above conditions existed. The nature of the disturbance cannot be determined from such evidence. They consider that former ideas concerning the relationship of such abnormalities to generally increased intracranial pressure must be abandoned because in some cases with markedly increased spinal manometric pressure none of the phenomena were present and in some cases the phenomena were marked when the spinal pressure showed no increase. Since these abnormalities indicate a lesion of the brain not always of a destructive nature he considers them probably due to local pressure. In separating supra- and subtentorial lesions he gives the following criteria: Patients with subtentorial lesions do not become nauseated, vomit or perspire, regardless of the amount of stimulation administered. Patients with supratentorial lesions are frequently quite susceptible, hence increased susceptibility of a patient to stimulation of the ear excludes the presence of a lesion in the posterior fossa but immunity from disturbances does not necessarily place the lesion subtentorially. He calls attention to the fact that normal persons may frequently be upset by stimulation of the ear, "therefore, this phenomenon, appearing during the examination of a patient, does not necessarily indicate the presence of a lesion of the brain, but it does indicate that if a lesion is present it is subtentorial." Susceptibility was particularly marked in lesions of the frontal lobe, the motor area, the temporoparietal area and the pituitary and suprasellar lesions. Susceptibility was absent in patients with

lesions of the temporal lobe, lesions of the occipital lobe and all sub-tentorial lesions. As to the side involved in cerebral lesions uncertain spontaneous pointing or uncertain past pointing of the arm or leg after stimulation indicates a lesion of the opposite side. Conjugate deviation may be present after stimulation to the side of the lesion. Interference with or absence of all vestibular responses from one ear indicates a lesion of the opposite side. Perversion of the nystagmus from the horizontal semicircular canal indicates a lesion on the same side. By means of these signs he was able to localize correctly as to side, 31 of 33 patients. The other 12 did not have lateralizing signs. In cerebellar lesions the side is indicated by uncertain pointing of the arm or leg on the same side; interference with or loss of all vestibular responses after stimulation on the side of the lesion; impairment of nystagmus from the horizontal semicircular canal on the same side; interference with responses from the vertical semicircular canals on the same side; and deafness on the side of the lesion. Of 6 cases 3 could not be placed as to side, 1 case was wrongly placed and the other 2 were correctly placed. In cases of lesions of the cerebellopontile angle the tumor was always found on the side on which the entire function of the eighth nerve was disturbed. The author then gives diagnostic complexes for each anatomic area and these groups of findings are definite enough to be of some localizing value. He concludes as follows: "A lesion of the brain usually causes abnormal reactions to the vestibular tests. Generalized increased intracranial pressure, as such, cannot be diagnosed by the vestibular tests. The vestibular observations indicative of the laterality of a lesion are definite and reliable, when present, but these signs are not exhibited in all cases of lesion of the brain. The vestibular tests can usually differentiate definitely between a supratentorial and a subtentorial lesion. Each anatomic area presents vestibular group observations of its own. While in the majority of cases the diagnosis of tumors of the brain can be made by the vestibular tests, their value would be the greatest when taken in conjunction with the general clinical observations." (The percentage of accuracy as presented in this study, if corroborated by clinical experience would make these new vestibular complexes extremely valuable adjuncts to our diagnosis of focal lesions.)

The Innervation of the Thymus.—PINES and MAJMAN (*J. Nerv. and Ment. Dis.*, 1929, 69, 361) present a study of the nerve supply of the thymus gland as found in mice, rabbits, cats and dogs. They find that the nerve bundles all enter the gland, extend through the interstitial tissue ramifying and following the tissue between the lobules. They gradually decrease in size and penetrate by means of thin bundles within the lobular septa of connective tissue. The thin nerve bundles along the vessels detach numerous fibers which form peculiar plexuses about the vascular walls. They differentiate two types of nerve plexuses, one in the adventitia of the vessels and the other within the medial tunic, these latter being the vasomotor nerves. As the vessels decrease in size the large nerve branches disappear and the thick nets become thin pearly threads and are covered with knobs. In the connective tissue between the lobules they find a terminal nerve apparatus of an ovoid or bulblike shape which they consider as a primitive receptive apparatus. The fibers from which they derive are thicker than the

vascular nerve fibers and do not show any varicosity. Certain of the vascular fibers they judge to be of cerebrospinal origin. They penetrate within the gland with the branches of the vagus. The nerve fibers penetrate also into the lobules and are diffusely spread throughout the parenchyma detaching lateral branches and terminal ramifications which end with small knobs adjacent to the cells. They consider those to represent the parenchymal nerve apparatus and to be closely related to the specific function of the gland. Hassal's corpuscles, they find surrounded outwardly by a nerve fiber widening along its limits or by terminal ovoid-like thickenings also adjacent to the inferior part of the tunic. They found no sympathetic ganglion cells. They conclude that the thymus gland is supplied with a thoroughly differentiated nerve apparatus. They find vascular nerves, sympathetic parenchymatous glandular nerve apparatus, and receptor apparatus. The whole innervating apparatus they believe to be partly of sympathetic and partly of cerebrospinal origin. "Thus the analysis of the nerve apparatus of the glands shows that all the elements of the tissue are under nerve control and nothing can occur within the gland without the regulation or registration of the activity by the nervous system." They conceive the receptor nerves as being stimulated by pressure at some stage in the secretory activity of the lymphoid lobules.

PATHOLOGY AND BACTERIOLOGY

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A Case of Periarteritis Nodosa.—GRAY (*J. Path. and Bact.*, 1929, 32, 787) adds another case description with necropsy findings to the number of about 127 reported cases of periarteritis nodosa. Although no vascular lesions were conspicuous on gross examination of the tissues, histologic inspection of the kidneys, liver, spleen and heart revealed a lesion of the smaller arteries and arterioles. The relatively more acute lesions predominated in the arterioles, where necrosis of the vessel wall, with or without swelling of the intima was surrounded by a cellular infiltration with a preponderance of polymorphonuclear leukocytes. The lesions of longer standing, such as were observed more often in the smaller arteries were characterized by a cellular thickening of the intima, often obliterating the lumen, a partial destruction of muscular and elastic tissue, and a cellular infiltration in and around the wall, the latter being composed in addition to many polymorphonuclear cells of a larger number of plasma and other mononuclear cells as well as fibroblasts, and a higher proportion of eosinophils. A finding of especial interest

in view of the existence of disease in the afferent arterioles and interlobular arteries, was the occurrence of extreme proliferation of endothelium in the glomerular tufts, narrowing most loops, obliterating others, associated with a hyperplasia of the cells of Bowman's capsule, which lead in some instances to the formation of typical crescents. No aneurysmal formations were found in any of the arteries.

Congenital Anomalies of the Liver.—MACMAHON (*Am. J. Path.*, 1929, 5, 499) reviews several cases. Many of the more common types are described and explained on an embryologic basis. The anomalies may be divided into two groups, in the first of which a retardation of development has occurred so that the liver or a part of it in the full term child resembles that of a developing fetus. The second group includes those cases of true developmental anomalies in which either the parenchyma or the connective tissue of the portal areas is involved. One type that is characterized by increase in number and dilatation of the periportal bile ducts, with an accompanying increase in the portal connective tissue may persist throughout life. With this anomaly is associated the congenital cyst of liver and frequently bilateral congenital cystic kidneys.

Allergic Inflammation in Kidneys.—HEPLER and SIMONDS (*Am. J. Path.*, 1929, 5, 473) produced allergic inflammation in the kidneys of rabbits previously sensitized subcutaneously to foreign proteins. The reaction produced was very rapid in occurrence and intense, an advanced acute inflammatory reaction with hemorrhage and early necrosis being present in twenty-four hours. Hemorrhage was found in all the injected kidneys when autopsied within seventy-two hours. The exudate was chiefly leukocytic with relatively little fluid. The necrosis was probably due to the direct toxic effect of the antigen on the sensitized tissue, it being absent about the hemorrhage in the nonsensitized rabbits.

Immune Cellular Reactions in Experimental Acute Peritonitis.—STEINBERG and SNYDER (*Arch. Path.*, 1929, 8, 419) experimenting with dogs, some of which had been previously immunized to *Bacillus coli*, found that in the first twenty-four hours following the production of fecal peritonitis the cellular reaction was predominantly polymorphonuclear. Bacteria in the peritoneal cavity were almost completely phagocyted in the immune animals at the end of eight hours. The action of the polymorphonuclear leukocytes in immune dogs was not specific, since they phagocyted other organisms as well as *Bacillus coli*. The difference in the cellular reaction of immune and nonimmune animals, they found to be quantitative. The immune dogs mobilized polymorphonuclears more rapidly and in far greater number than did the nonimmune.

Traumatic (False) Aneurysm of the Aorta.—Traumatic rupture with subsequent false aneurysm formation of the aorta is perhaps most apt to occur in the regions of relative fixation, two finger-breadths above the semilunar cusps and at the level of insertion of the ductus arteriosus. SHENNAN (*J. Path. and Bact.*, 1929, 32, 795) reports a case of traumatic

aneurysm below the latter region at the level of origin of the fifth pair of intercostal arteries, occurring in a man, aged fifty-seven years. The patient, who had been knocked over by a bicycle, presumably falling on his chest and shoulder, lived for eight weeks to die of rupture of the aneurysm into the esophagus. The aortic arch presented a small amount of atheroma. Between the fourth and sixth aortic intercostals an irregular opening existing in the posterior wall, measuring 3 cm. transversely and 1.2 cm. from above downward, led into a cavity lined with irregular antemortem thrombus opening into the esophagus. Microscopic examination of the wall of the aorta at a short distance from the aneurysm showed evidence of hyaline and fatty degeneration with calcareous deposits.

Typical Lesions Produced in Animals by a Strain of Sporothrix Found in Well Water.—CATANEI (*Comp. rend. Soc. de biol.*, 1929, 101, 447), with a strain of sporothrix found in well water, and which differed morphologically from the *Sporothrix beurnmanni*, was able to produce experimental lesions in guinea pigs, mice and in a monkey, which were sometimes fatal and showed the anatomic pathologic characters analogous to those in the lesions of human sporotrichosis.

Growth of *Bacillus Tetani* in Suspensions of Agar.—Agar is so commonly used in bacteriologic media in a relatively high amount that little attention has been paid to its use in relatively small quantities. BELIN (*Comp. rend. Soc. de biol.*, 1929, 101, 435) declares that 0.1 per cent agar makes a suspension exactly intermediate between a solid and a liquid media and favors very considerably the growth of *Bacillus tetani*.

Late Gross Lesions in the Aorta and Pulmonary Artery Following Rheumatic Fever.—GRAY and AITKEN (*Arch. Path.*, 1929, 8, 451) present 4 cases of rheumatic fever in which gross lesions, believed to be of rheumatic origin, were found in the aorta and pulmonary artery. One case showed false aneurysm of aorta. Each case had a clinical history of one or more attacks of rheumatic fever or of chorea or of repeated attacks of tonsillitis. Each had typical rheumatic lesions in the heart and the possibility of syphilis was ruled out by absence of any evidence of it in the history, serologic reaction or in the gross or microscopic appearance of the aorta and other organs. The gross lesions of aorta consisted of a fine stippling of the intima sufficiently marked in one case to give a honey-comb appearance. The intima and adventitia in these areas were thickened and the media markedly thinned. The authors emphasize an eccentric fibrosis of the veins as being rheumatic. Gross scars observed in two cases were believed to be due to thrombosis of vasa vasorum in the course of a rheumatic process. The aneurysm described is also explained on a rheumatic basis. It is partly of dissecting type and partly false. The dissection had split the media. The intima and adventitia were markedly thickened but the intima except for the opening into the aneurysm was smooth and showed no gross lesion.

HYGIENE AND PUBLIC HEALTH

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The Effect of Sun and Air and Air Baths on the Respiratory Gaseous Exchange in Man.—JAKOWENKO (*Am. J. Hyg.*, 1929, 10, 165) states that the respiratory metabolism, determined in an individual after a fast of twelve hours and after an hour's rest in bed in a health resort, is in the majority of cases increased on comparison with Harris-Benedict's normal figures. The conditions and the life in a health resort (light clothes, air and sun baths, sea bathing, emotions) are as a rule sufficient to produce an increase of the metabolism in the majority of people. However, there are some whose respiratory exchange does not rise in similar surroundings above Harris-Benedict's figures. During air and sun baths and during air baths the gaseous exchange in man tends to show a further increase. In certain conditions this metabolism may decrease below the level of basal metabolism, which had been observed in the same person before the bath. The height of the respiratory gaseous exchange in man during air and sun baths and air baths depends among others on the combination of meteorologic conditions, either producing a relatively strong cooling of the human body or favoring an increase of heat in it; these factors are: temperature, humidity, air movement and the intensity of solar and skylight radiation. Among all the climatic factors which favor the cooling of the body and the increase of gaseous exchange in man during air baths on the beach, the rate of air movement is of the greatest importance. Besides these external factors, there are also internal constitutional factors, which determine the amplitude of fluctuations shown by the gaseous exchange of man at the health resort. All the climatic factors may be divided into 2 groups according to their effect on the gaseous exchange in man: (1) Those increasing the gaseous exchange, apparently due to the irritation of the peripheral cutaneous nerve endings of the sympathetic nervous system, such as low temperature and air movement, and (2) those factors which decrease the gaseous exchange (high air-temperature, absence of air movement and excess of heat produced by solar radiation). The writer believes that a moderate increase in the gaseous exchange of man should be the purpose of climatic treatment. The latter proves to be beneficial to a diseased and exhausted body, due to its production of an increased activity of specific vegetative organs (the liver, the heart, and so forth), that of the endocrinous system and of the oxidating processes in the tissues.

Preparalytic Poliomyelitis. Further Observations on Treatment with Convalescent Serum.—AYCOCK and others (*J. Infect. Dis.*, 1929, 45, 175) treated 116 cases of preparalytic poliomyelitis with human convalescent serum. The outcome of these cases as measured by case fatality rate, percentage of cases which developed no paralysis, percentage of cases which developed paralysis of the two severe grades, as well as by the average amount of paralysis per case was strikingly different from the outcome of untreated cases in the same outbreak. That this difference was not due in any great degree to the inclusion among the treated cases by reason of early diagnosis of milder forms of the disease, which are ordinarily missed, was indicated by the close correspondence between the results in the state at large and in Watertown-Waltham, where there were increased opportunities for detecting milder forms of the disease and where a larger portion of all cases was seen and treated. A relatively enormous number of missed cases must be assumed to have occurred in order to equalize the outcome of treated and untreated cases. A house to house canvass in one locality where the disease was prevalent failed to disclose the occurrence of any number of missed cases. All treated cases presented typical signs and symptoms of preparalytic poliomyelitis. The subsequent occurrence of some paralysis in 61.2 per cent of the treated cases indicated that a nonparalytic form of the disease was not being dealt with. Twenty-three per cent of the cases which developed no paralysis were of the so-called dromedary type as compared with 26.8 per cent of the cases which did develop paralysis. Since the dromedary phenomenon is peculiar to poliomyelitis, this is regarded as an additional substantiation of the diagnosis in the group of cases in which no paralysis developed. Of the 143 patients seen as suspected preparalytic poliomyelitis, who were excluded, the majority subsequently were found to be suffering from other conditions. In only 8 cases could the suggestion of abortive (not preparalytic) poliomyelitis be considered.

Sinusitis and Otitis in Swimmers.—SAUNDERS (*Am. J. Hyg.*, 1929, 10, 253) states that the value of swimming as a means of exercise more than compensates for its dangers for the normal individual. Furthermore, the dangers can be greatly lessened. Matters that especially require attention are means of reducing trauma to the nose and ears and correct habits of breathing. Accordingly, methods of plugging the nose are worth attention. In high and fancy diving this is useful. The use of an oil spray in the nose before entering the water has been suggested by Skillern and others. This helpful measure is almost universally neglected. Persons with narrow nasal passages, deviated septums and other anatomic abnormalities are much more prone to infection than those who have unobstructed sinus drainage. This leads to the suggestion that all persons wishing to do diving and polo first have a nasal examination, with subsequent medical or surgical treatment if indicated. To these local measures of reducing trauma and consequently the likelihood of bacterial invasion should be added the general measure of supervision of the length of the swimming period. Forty-five minutes in the water is probably long enough. There is evidence that bodily resistance is reduced with exposures longer than this. Correct habits of breathing are of major importance. Breathing in

swimming is just the reverse of that in any other activity. Inhalation is always through the mouth while exhalation should be done through both the nose and mouth simultaneously. The latter is difficult but is well worth learning. It is impossible to exhale with sufficient rapidity through the nose and if the mouth is used exclusively water flows into the nasal passages.

Streptococci From Cases of Epidemic Septic Sore Throat, Scarlet Fever and Erysipelas.—WHEELER (*J. Prev. Med.*, 1930, 4, 1) studied the cultural, biochemical and serological reactions of hemolytic streptococci isolated from outbreaks of septic sore throat in Wayland and Savannah, N. Y. In the Savannah outbreak, the streptococci isolated from patients and from milk from the infected udder of a cow supplying milk to these persons were found to be identical in all respects. The majority of the strains isolated from both of these epidemics gave the cultural and biochemical reactions of "*Streptococcus epidemicus*." The study of the toxin production and agglutination reactions of streptococci isolated from these two epidemics and from two other outbreaks of epidemic septic sore throat, as well as the demonstration of well-defined capsules on streptococci isolated from typical cases of scarlet fever and erysipelas, indicate that the streptococci associated with epidemic septic sore throat, scarlet fever and erysipelas cannot, by any method now available, be separated into specific groups.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 17, 1930.

Alteration in Response to Insulin During Experimental Leukocytosis.—ISOLDE T. ZECKWER (from the Department of Pathology, University of Pennsylvania). The purpose of the experiments was to learn what factors are involved in the altered response to insulin which may be observed during acute infections in diabetic patients. For the present, the experiments were limited to a study of the effect of leukocytosis induced by a chemical rather than a bacterial irritant, in normal rabbits.

Each of 8 rabbits, under standard conditions, was injected on several occasions with a small convulsive dose of insulin. Then an intense leukocytosis was induced by intravenous injection of 0.1 gm. sodium nucleinate. In 5 rabbits during the period of leukocytosis, at about eighteen hours after injection of the nucleinate, the previously convulsive dose of insulin no longer induced convulsions. These rabbits were allowed to return to normal conditions, when the same dose again caused convulsions. On again inducing leukocytosis by nucleinate, convulsions were again inhibited.

When sodium nucleinate is repeatedly injected the bone marrow becomes exhausted of its myeloid elements, so that a rise in circulating leukocytes no longer occurs. When rabbits which had previously showed insulin inhibition during leukocytosis were brought to the stage where sodium nucleinate no longer caused leukocytosis, convulsions again occurred, when the same dose of insulin was given, as though no nucleinate had been injected. This would appear to indicate that inhibition of insulin action had occurred because of leukocytosis. The blood sugar just before the insulin was injected was within the normal range in the rabbits so far described.

In 3 rabbits no inhibition of insulin action occurred during nucleinate leukocytosis, but in these rabbits the blood sugar was low just before the injection of insulin, about eighteen hours after the injection of the nucleinate.

In the intact rabbit sodium nucleinate injected intravenously caused an abrupt rise in blood sugar, with a maximum at about one hour, followed by a fall to normal or slightly below. The rise did not occur if, some time previous to the injection, one adrenal was excised and the opposite splanchnic nerve cut. Insulin inhibition could be induced during nucleinate leukocytosis in 2 rabbits in which glycogenolysis was prevented by such an operation.

Since insulin is inactivated *in vitro* by the enzymes of leukocytes, it is considered probable that the insulin inhibition during nucleinate leukocytosis is dependent upon the enzymes of the circulating leukocytes.

Penetration of Antibodies into the Central Nervous System of Rabbits.—JULES FREUND (from the Henry Phipps Institute, University of Pennsylvania). In passively immunized rabbits antibodies (agglutinins against typhoid bacilli) penetrate into the cerebrospinal fluid even in the absence of inflammation of the meninges. The penetration proceeds slowly; it is finished only several hours after the injection of immune serum. When the penetration is completed the ratio of the titer of serum to that of the cerebrospinal fluid is equal to 100 to 0.3.

The accumulation of antibodies in the brain and spinal cord is finished within fifteen minutes. The ratio of the titer of the serum to those of the extracts of these organs is similar, that is, about 100 to 0.7 (1 cc. of serum compared with extract prepared from 1 gm. of organ). The antibodies cannot be removed from the brain by perfusion.

When antibodies are injected into the cisterna magna, they penetrate into the blood at once, but they remain in the cerebrospinal fluid in excess for one day. Three days after the injection the ratio of the antibody titer of the serum to that of the cerebrospinal fluid is about the same as in rabbits immunized by the venous route. (See previous papers of this series in *Journal of Immunology*, 1927, 1928, 1929.)

Progress in the Characterization of Antibody Action.—S. MUDD, B. LUCKÉ, M. McCUTCHEON and M. STRUMIA (from the Henry Phipps Institute and the Department of Pathology, University of Pennsylvania). We have undertaken analysis of the mechanism by which blood serum promotes the phagocytosis of bacteria or other foreign particles. Methods have been developed in these laboratories and elsewhere by

which the properties of bacterial surfaces can be studied directly and the changes effected in them by contact with serum can be ascertained. A quantitative technique for the study of phagocytosis *in vitro* has been developed, using the improved apparatus of O. H. Robertson. Study of the bacterial surfaces and of phagocytosis has been conducted simultaneously upon the same combination of bacteria and serum.

Sera which promote phagocytosis of bacteria have been found invariably to cause certain definite changes in the surface properties of the bacteria, namely increased cohesiveness, decreased surface potential difference and increased resistance to wetting by oil. Similarly, but with certain exceptions, sera which cause these characteristic changes in the bacterial surfaces also promote phagocytosis. The phagocytosis-promoting, agglutinating and surface effects are in quantitative correspondence. A similar striking correspondence has been found between the agglutinating, surface and phagocytosis-promoting effects caused by the euglobulin and pseudoglobulin fractions of antibacterial sera.

Following the technique of F. S. Jones, collodion particles have been coated with precipitinogen and then treated with homologous precipitin sera and their protein fractions. The same sera and serum fractions cause specific precipitation, agglutination or phagocytosis according to the conditions under which they are allowed to react with antigen.

Agglutinating, surface and phagocytosis-promoting effects have thus been found to be quantitatively parallel. This quantitative correspondence of the several effects of a serum or serum globulin fraction has been found both for antibacterial and for antiprotein sera and their globulin fractions. All of the effects are consequences of the deposit of sensitizing serum substances on the antigen surface. The surface deposit so produced by maximal sensitization has similar properties, whether deposited upon acid-fast bacteria or upon precipitinogen-coated collodion particles, that is, the sensitized surface has wetting properties characteristic of protein, is cohesive, and has an isoelectric point between pH 5.5 and 5.8. These are the properties also found for specific precipitate.

These studies thus bring evidence of a new sort in support of the following simple generalization: The combination of antigen and antibody is determined by specific chemical affinities. The effects following this combination, namely precipitation, agglutination, changes in surface properties and phagocytosis, are consequences of the properties primarily of the antibody-protein combined with and deposited upon the antigen surface.

Fixation of Iron by an Inflammatory Reaction.—VALY MENKIN (from the Henry Phipps Institute, University of Pennsylvania). It has recently been demonstrated by the writer that a vital dye such as trypan blue when injected intravenously rapidly accumulates in an inflamed area and is fixed there so that the dye fails to reach the draining regional lymphatic nodes. Subsequent quantitative work showed that the rapid accumulation of dyes in inflamed areas is the result of increased capillary permeability with inflammation.

Having established this principle with a dye, further studies were then undertaken to see whether a metal would be fixed *in situ* by the inflammatory reaction. Iron was selected because of the ease of detect-

ing this metal qualitatively in tissues by the Prussian blue reaction. Colloidal iron or ferric chlorid when injected into the normal peritoneal cavity of rabbits rapidly accumulates in the retrosternal lymph nodes as evidence by the Prussian blue reaction. When, however, this metal is injected into an inflamed peritoneal cavity caused either by aleuronat or *Staphylococcus aureus*, the iron is fixed *in situ* and fails to reach the retrosternal lymph nodes. Quantitative studies of iron content of these lymph nodes in animals injected intraperitoneally with ferric chlorid reveal 56.7 per cent more metal in the nodes of animals with normal peritoneal cavity than in those with inflamed peritoneal cavity.

Experiments were then performed to demonstrate the accumulation of the metal in inflamed areas when ferric chlorid is injected into the circulating blood stream. Acute inflammatory reactions of six to seven hours' duration were obtained by the injection of *Staphylococcus aureus* into the dermis of the abdomen of rabbits. Such acute inflamed areas do not give the Prussian blue reaction *per se*, but when ferric chlorid is injected intravenously the metal accumulates in these areas and becomes demonstrable by the qualitative test. Quantitative determinations of iron content of inflamed areas of animals that received no iron show as an average figure 9.7 mg. per 100 gm. of dry tissue as compared with 16.2 mg. in animals injected intravenously with ferric chlorid. There is, therefore, in inflamed areas an increase of 67 per cent in the iron content by the intravenous injection of the ferric salt. The average iron content of normal skin areas in injected animals is 10.4 mg. as compared with 8.4 mg. in noninjected animals. This shows an increase in normal skin of 23.8 per cent by the injection of the metal. Hence there is about three times more metal accumulating in inflamed than in normal skin areas. These findings show that iron, like trypan blue, accumulates in an inflamed area when injected intravenously and is fixed there by the inflammatory reaction.

These studies may have clinical applications. It is conceivable that by the accumulation of dye, iron-containing, or other substances in an inflamed area, the character or course of development of the inflammatory reaction may be altered.

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RICHARD MILLS PEARCE, JR., M.D.

RICHARD MILLS PEARCE, JR., M.D., D.Sc.

IN recent years few men have exerted so wide an influence on medical education as did Dr. Richard Mills Pearce, Jr. His untimely death in New York City on February 16, 1930, deprived the medical profession of one whose interest, energy and ability had long been dedicated to progress in medical research and the advancement of medical education. As General Director of the Division of Medical Education of the Rockefeller Foundation, a post which he so ably graced from 1920 until his death, Dr. Pearce's activities as an educator were not limited to this country; they were international. The Far East, South America and many of the countries of Europe, notably Poland, England and France, all profited by his wise counsel and ripe experience. Whenever medical institutions on this continent sought to benefit by the help and support of the Rockefeller Foundation, it was invariably his judgment and advice that proved the determining factors.

Born in Montreal, Dr. Pearce received his early education at the Boston Latin School, and his degree in Medicine from Harvard University in 1897. From the beginning of his career he manifested little desire to practise medicine, and turned his attention to pathology. As Resident Pathologist to the Boston City Hospital and Instructor in Pathology to the Harvard Medical School his industry and ability soon attracted the attention of such eminent pathologists as Councilman, Welsh and Flexner. In 1900 Dr. Pearce came to the University of Pennsylvania as one of Dr. Flexner's assistants and not long thereafter he became Assistant Professor of Pathology in that institution. In 1903 he went to Albany, N. Y., as Professor of Pathology and Bacteriology in the Albany Medical School, and at the same time carried on the duties of Director of the Bender Hygienic Laboratory, as well as those of Director of the Bureau of Pathology and Bacteriology of the New York State Department of Health. Five years later Dr. Pearce was made Professor of Pathology in the University and Bellevue Hospital Medical College in New York City. In 1910 he was called back to the University of Pennsylvania, to become the first Professor of Research Medicine in that institution. For one year after his return to the University

of Pennsylvania he was also Professor of Pathology. From that time on until he became associated with the Rockefeller Foundation, ten years later, his entire time was devoted to the successful conduct and development of the new department of Research Medicine. Shortly after the United States entered the World War he was commissioned a Major in the Medical Corps of the Army. In 1918 Dr. Pearce assumed the arduous duties of Chairman of the Medical Division of the National Research Council; his noteworthy accomplishments in this capacity are a matter of record.

It was during the trying days of the World War that Dr. Pearce undertook the temporary Editorship of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES. When the call to active military service made it impossible for those who were editing this Journal to continue their work, it was Dr. Pearce who, with characteristic unselfishness, voluntarily assumed their duties without thought of recognition or recompense. The readers of the JOURNAL can testify to the able way in which that publication was conducted under his direction. At this time it is but fitting that the publishers, as well as those who were then editors of the JOURNAL, should again express their deep and sincere appreciation of the man who so generously rendered such timely and efficient help to them and to the AMERICAN JOURNAL OF THE MEDICAL SCIENCES.

Known throughout the civilized world as a distinguished scientist, teacher, author and educator, Dr. Pearce occupied a position in medicine that cannot readily be filled. His death is an irreparable loss. Nevertheless, to those who have had the privilege of knowing him, it is both a consolation and a satisfaction to realize that his achievements in the field of medical education will live on, and that the years to come, even more than the present, are destined to prove the farsighted wisdom of his constructive policies.

GEORGE MORRIS PIERSOL.

THE
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ORIGINAL ARTICLES.

CHRONIC MENINGOCOCCUS SEPTICEMIA.

(CHRONIC MENINGOCOCCEMIA.)

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GWYN, in 1898, stated that up to that time the meningococcus had not been demonstrated in the general circulation and that it had not been known to play the part of a general infective agent. With these preliminary remarks he proceeded to report the first instance in which the meningococcus was found in the peripheral blood. The patient was on Dr. Osler's service, admitted with the diagnosis of typhoid fever. This first case of meningococcus septicemia was one of the acute variety with clinical signs of meningitis on the second day and death on the sixth.

It remained for Soloman, in 1902, to point out first the chronic variety of meningococcus septicemia, that type which lasts several months and in which meningitis does not play so prominent a part or in which it frequently is absent. It is to this type that the following remarks are essentially directed, and it is our intention to review the subject and report a case. Since Soloman's paper many cases of chronic meningococcus infection with very late or no meningeal localization have been described, especially in the French literature. Comparatively little reference is made to this type of the disease in the standard medical textbooks and in English medical

literature. However, in the following classification of meningococcus meningitis, Sir Humphrey Rolleston does give it a distinct place:

1. Fulminating.
2. Ordinary acute.
3. Abortive:
 - (a) Septicemic.
 - (b) Meningitic.
4. Chronic:
 - (a) Cases not treated, or unaffected by treatment.
 - (b) Septicemic.
 - (c) Encysted or loculated meningitis, including posterior basilar meningitis.

In describing 4(b) he states that meningococcus septicemia may precede, follow or occur without meningeal infection and may suggest malaria or enteric fever.

The title, "Epidemic Cerebrospinal Meningitis," which tends to direct all concern to the meninges and ordinary form of the disease, is the reason given by one author for the neglect and scant notice given to the extrameningeal forms of meningococcus infection and Herrick advocates abandoning the above name on this account. Indeed, the number of cases of meningococcus infection not developing meningitis is sufficiently large to demand consideration.

Netter had observed the chronic septicemic type in 5 of 368 cases of meningococcus infection and even relatively more common in private cases—3 out of 90 (3.3 per cent). We believe this form of the disease sufficiently different from the acute variety to warrant separate consideration.

Case Report. Mrs. S. K., aged forty-three years, born in Russia, was admitted to the Beth Israel Hospital on May 11, 1927, complaining of feverishness and headache of four days duration. She stated that for the past four days she had been feeling feverish in the afternoons while in the mornings and evenings this temperature discomfort had not been present. On two occasions, four and three days before admission, she experienced definite rigors. The headache which also came on suddenly with the fever was rather severe. It was almost constant and referred to the whole head.

The past history and family history otherwise were not relevant to the present illness.

Upon admission to the hospital, the patient did not appear very ill but rather seemed to be quite comfortable lying in bed. The temperature was 101° F., pulse, 90 and respirations, 20.

Examination of the head was negative. There were no abnormal neurologic findings. The throat was not congested. Heart and lungs were also normal to the usual methods of examination. Splenic dullness could be made out to extend to the costal margin and on palpation the edge of the spleen could just be felt under the costal arch.

Over the abdomen, back and extremities, there was a diffuse erythematous eruption consisting of small slightly raised, tender, infiltrated, reddened spots ranging from 2 to 15 mm. in diameter. Outside of slight pain or

achiness on motion of knees and elbows, examination of joints was negative. The rest of the general physical, as well as neurologic, investigation proved unyielding.

The results of the laboratory tests were as follows:

The examination of the blood revealed 3,650,000 erythrocytes per c.mm. and 65 per cent hemoglobin (Sahli). There were 8400 leukocytes per c.mm., of which the polymorphonuclears constituted 80 per cent; lymphocytes (small), 18 per cent; transitionals, 2 per cent. Of the polymorphonuclears 2 per cent were eosinophils and 4 per cent were nonsegmented forms. No parasites or abnormal cells were observed. The blood was Type 2 (Moss). The Wassermann, Felix Weil and Widal tests (including tests for paratyphoid A and B), and blood culture were all negative. The blood chemistry was: Urea nitrogen, 10; nonprotein nitrogen, 22; creatinin, 1; blood sugar, 100 mg. per 100 cc. of whole blood. The van den Bergh reaction proved negative on the direct test and gave a reading of 0.3 units on the indirect. The blood serum registered an icteric index of 2.5 units. The urine revealed no abnormalities on routine examination. Roentgenogram showed the lungs to be clear.

The patient's condition remained practically unchanged for four to five weeks. The fever during this time reached 101° to 104° F. daily and was intermittent. The pulse rate not quite proportional to the fever, ranged from 90 to 100. During this period there were frequent recurrences of the eruption on the body, extremities, palms of the hand and soles of the feet—crops appeared to come out with the rise in temperature and lasted several days, fading and leaving a discoloration.

Prostration finally began to develop and a slight jaundice appeared.

Two transfusions were given with very little effect.

On June 3, twenty-seventh day of illness, a blood culture was reported to have 25 colonies on a plate. These bacteria were Gram-negative diplococci and had cultural characteristics of the meningococcus on differential sugars. This blood culture was the fifth taken and was performed with the same routine technique (unenriched media). Three days later, spinal fluid examination for meningococci was negative.

Except for the temperature the patient appeared to be fairly well clinically up to June 14—thirty-eight days after the onset the patient began to complain of headache in the morning. At 2 P.M. she suddenly became comatose. The neck was distinctly rigid; pupils were dilated, the right greater than the left. There was no Kernig or Babinski sign. Spinal tap showed the fluid to be under increased pressure; 25 cc. of cloudy fluid were removed and 25 cc. of an antimeningococcus serum were injected.

June 15: Again after removal of spinal fluid 20 cc. of serum were injected intrathecally—the patient seemed to respond slightly.

June 16: 17 cc. antimeningococcus serum given intrathecally.

June 17: 30 cc. spinal fluid removed—fluid is clearer. Twenty cubic centimeters of serum given (a specially concentrated antibody solution furnished by New York City Board of Health).

June 18: 50 cc. antimeningococcus serum given intravenously.

June 19: 50 cc. antimeningococcus serum given intravenously.

June 22: Condition very low, pupils dilated, do not react readily, eyes bulging and starey, patient is irresponsive. There is a marked Kernig sign and increase in nuchal rigidity. Forty-five cubic centimeters of cloudy spinal fluid removed, 20 cc. of serum given intrathecally. Fifty cubic centimeters of serum given intravenously.

June 23: 60 cc. antimeningococcus serum given intramuscularly; 40 cc. spinal fluid withdrawn and 20 cc. serum introduced. This the specially concentrated antibody solution. Coma deepened. At 9.45 patient had a convulsion, then ceased to breathe.

Additional Laboratory Data:

	Blood count.							
	R.B.C.	Hb.	W.B.C.	Neutr.	Eosin.	Nonseg. poly.	Small lymph.	Trans.
May 12 . . .	3,650,000	65	8,400	74	2	4	18	3
May 14 . . .	3,450,000	..	11,400	75	1	7	15	2
Transfusion 500 cc.								
May 18 . . .	3,700,000	70	16,100	61	..	20	18	
May 23 . . .	3,950,000	60	12,000	83	..	2	17	
June 4 . . .	3,900,000	65	10,500	81	..	8	19	
Transfusion 500 cc.								
	4,050,000	..	11,000	76	..	9	13	2
	3,300,000	65	10,000	74	1	5	18	2

Blood Cultures. May 11: Sterile. (One blood culture taken outside of hospital—sterile.)

May 16: Sterile.

May 23: Sterile.

June 3: Twenty-five colonies per plate (twenty-seventh day, Gram-negative diplococci).

Cerebrospinal fluid.

	Pressure.	Albumin.	Glob.	Cu. red. subst.	Bact.
May 24 . . . Clear	..	Trace	0	0.04	
June 6 . . . Secondary	..	2+	2+	0.04	
June 15 . . . 6000	2+	2+	} Meningo- cocci.
June 16 . . . 1040	2+	2+	
June 17 . . . 1300	3+	3+	2+	..	
June 21 . . . 2300	3+	3+	..	None	
June 23 . . . 6100	3+	3+	3+	None	

Spinal Wassermann, negative.

Discussion. Chronic meningococcus septicemia is usually characterized by a rather sudden onset. Headache, fever and joint pains is the patient's complaint. The headache is neither severe nor has it a particular localization. It may be frontal or it may be present all over the head and is usually constant. The fever is of the intermittent type, ranging from 99° to 102° or 104°, and continues as such throughout the course of the illness, at times with afebrile periods of four to six days. Netter has carefully described the febrile reaction and has some temperature charts which closely simulate the paludal type of intermittent fever. One of Dock's cases had seven consecutive tertian paroxysms of fever.

Joint pains with or without swelling and redness of the joint, may be a prominent feature of onset and range much in severity. While a 10 per cent complication in the acute disease, it is much more frequent in the chronic condition (43 of 68). An arthritis difficult of differentiation from acute articular rheumatism may present itself. With headache, fever and joint pains as the only complaint

and but slight prostration, the disease continues. During the first week, and often during the subsequent course, at irregular intervals and at irregular times, the patient may have chills—true rigors numbering from two to a half dozen or more in all. By the end of the first week a somewhat characteristic rash appears and this quartet of headache, intermittent fever, joint pains and characteristic rash is sufficiently labeling and identifying to some French authors to permit the presumptive diagnosis of chronic meningococcus septicemia.

Other less common modes of onset are as a focal infection such as a tonsillitis, sinusitis, arthritis, or meningitis. At times a slow insidious onset (Merklen, Wolf, Froelich) may inaugurate the illness.

Cases may be part of an epidemic or they may be sporadic. The disease is more prone to occur in adults and especially in males. Of 27 cases of meningococcus septicemia (acute and chronic) reported by Cholier, Giraud and More, only 4 were in females and three-quarters were between the ages of twenty and thirty years. Late spring and early summer are the seasonal preferences.

Physical Examination. The patient early in the disease does not appear acutely ill, but rather quite comfortable and he may not even be confined to bed. The rash is quite prominent. It appears during the first week, though not necessarily so. Four of Netter's 5 cases never had a skin eruption, but most of all the other's cases reported did (Soloman, Vignot, Herrick, Morgan, Neergaard, Dock, and so forth). The rash is of the multiform erythematous type, consisting of crops of firm, tender, slightly raised, red to bluish-red nodules from 0.25 to 2 cm. in diameter. They are found especially on the extremities and trunk and occasionally on the face. They tend to fade after several days and then recur. Frequently new crops come out with each rise of temperature and these may last only twelve hours. They have been noticed to disappear with the onset of meningitis. The skin lesion has been likened to erythema multiform with a marked nodose element (Netter). It does not, however, leave the bluish discoloration on disappearance as does erythema nodosum (Morgan). Other types of skin manifestations found are erythema multiforme, erythema nodosum, purpura, petechiæ, lenticular rose spots (Netter) and herpes. Two types of skin lesion may be present together. The rash is possibly due to cutaneous emboli of meningococci (Rolleston and Renault and Cain) or to toxic effect on the capillary endothelium.

Further examination at this early stage usually shows the absence of any signs of meningitis. There is no nuchal rigidity and the Kernig sign is not obtainable. Eyes and the cranial nerves prove to be normal on examination. The accessory sinuses of the head have not been sufficiently studied in these cases to make general statements concerning them. Herrick reports meningococci in empyema of the accessory sinuses. His case number three of sub-

acute meningococcus sepsis without meningitis started with a tonsillitis and sinusitis. The infected sinus was punctured and drained and though no culture of the pus was made, from further observations the infection was probably of meningococcic etiology. His case number six also was one of sinusitis with rash and no meningitis. Here culture of the sinus pus revealed meningococci.

An acute or subacute tonsillitis and pharyngitis is a not infrequent finding, but there are not sufficient reports on cultures from the tonsils and nasopharynx in these cases to draw conclusions as to their infection by the meningococcus. Are they the portal of entry for the chronic sepsis?

Pulmonary involvement in chronic meningococcemia does occur. Meningococcus pneumonia is said to differ from the ordinary pneumococcic type of primary lobar and bronchopneumonia in having a more insidious onset and it is claimed not to produce pain in the side. Meningococci have been found in the sputum of some cases. Pulmonary infarcts and pulmonary abscesses have been found due to inflammatory thrombosis of a branch of the pulmonary artery and the meningococcus has been obtained from the clot in the artery. In a case of bronchopneumonia following measles, Chickering has recovered the meningococcus by lung puncture.

Casting some doubt on meningococcus pneumonia, Zinsser states that reports of meningococci in bronchial secretion from bronchopneumonia and lobar pneumonia have usually been based upon insufficient bacteriologic evidence.

Of the cardiac complications, endocarditis, pericarditis and myocarditis have been described. Cecil and Soper, in 1911, were able to find 4 cases of meningococcus vegetative endocarditis in the literature. Krumbhaar added 3 in 1918, from the war epidemic. Roads, in 1927, after a careful survey of the literature was able to locate 11 cases most of which were of the acute variety of the disease, though some lasted five to twelve weeks (Mackarell). In some of these cases vegetations with meningococci were found on the mitral and aortic valve. Meningitis was not present in the majority. These cases are considered essentially endocarditis, that is, valvular heart disease due to the meningococcus. Meningococcus myocarditis is extremely rare. Pericarditis is not a very uncommon complication.

The spleen is frequently enlarged; and in most cases sufficiently so to be easily palpable. In 11 cases of both the acute and chronic form of meningococcus septicemia the spleen was enlarged in 9 (Chalier, Giraud and More). Nine of 68 cases collected by Dock had splenomegaly.

Joint manifestations range from mild fleeting arthralgia with no other local signs, to purulent arthritis with markedly swollen and reddened joints. This disturbance comes on early in the disease and rarely does it persist throughout the entire course of the disease although the signs may come and go. The joints of the lower ex-

tremities are the ones most often involved. Several are affected at one time and the involvement tends to be migratory. The purulent type is apt to be localized to one joint.

Laboratory Data. Examination of the blood shows a mild to moderate leukocytosis ranging from 10,000 to 15,000. In the cases to be reported, blood counts were taken throughout the course of illness and they ranged from 8400 to 16,100. The percentage of polymorphonuclears was between 70 and 80. Anemia is not marked, the number of red blood cells rarely being greatly diminished. Hemolysis, as evidenced by the van den Bergh test was not indicated in our case. The icteric index was 2.5 and the indirect van den Bergh normal.

It is interesting to note that blood cultures taken early in the disease and even during the first three weeks most frequently reveal no growth. In some cases this may be due to the failure to use properly enriched culture media, but certainly not so in all. In Dock's 68 collected cases, meningococci were found in the blood in 41—15 only when enriched media was used; in 10, cultures were repeatedly sterile; of these 10, enriched media was utilized in 2. In Morgan's first case, the blood culture was positive only on the forty-ninth day of illness and in the second case on the thirty-ninth day. This was the sixth culture. Neergaard reports the cultures positive on the thirty-first and forty-first day. In the following case growth was first obtained on the twenty-seventh day of illness.

A sterile culture, especially one on ordinary media, does not exclude the presence of a bacteriemia. For cultivation of the meningococcus one should use media enriched with blood serum or ascitic fluid, remembering that the meningococcus is practically an obligatory aërobe and grows best at 37° C. and neutral reaction. Without transplants the culture remains alive but a short time. In serum agar the organism may die out in two to three days. Exposed to sunlight and drying the culture will die in twenty-four hours.

Microscopically the Gram-negative intracellular and extracellular diplococcus of Weichselbaum may closely resemble the gonococcus. In making the differential diagnosis, observance of the marked individual size variation of former is of help. With the Neisser stain metachromatic granules in the center of the cell bodies of the meningococcus may be demonstrated. These two organisms should also be separated by their different actions on the sugars. The meningococcus ferments both dextrose and maltose. The gonococcus ferments dextrose but not maltose.

While these methods are helpful, agglutination tests are desirable and add conclusiveness to the diagnosis. The organisms cultured from the patient should be agglutinated by a polyvalent antimeningococcus serum in various dilutions. Some antimeningococcus sera from horses may agglutinate homologous strains in dilutions of 1 to 3000 and other meningococci in 1 to 500 dilutions. Occasionally

the organisms first isolated may prove inagglutinable, while subcultures are agglutinated. Prolonged incubation has been shown to disturb the specificity of agglutination.

The patient's blood serum can be examined for antibodies by agglutination tests with meningococci. In one case meningococci were agglutinated by patients serum in dilution of 1 to 400.

As for the urine, findings, such as albumin, attributable to the fever, may be present. It is extremely rare to find the meningococcus in this fluid, however Netter did obtain this organism on culture of urine withdrawn from the cadaver on three occasions.

The spinal fluid, in cases where signs of meningitis were not present, was normal to every examination. It is considered inadvisable by some to perform a spinal tap in the absence of definite signs of meningitis or strong suspicions thereof. The danger lies in stirring up invasion of the meninges by the organisms already present in the blood stream, because of the disturbance in osmotic relationship between the two fluids and also possibly through the direct local mechanical trauma caused by the lumbar puncture. This, however, is not in agreement with Dock's findings. The cases where meningitis was present, showed typical spinal-fluid findings of meningococcus meningitis. However, the reducing substance, "sugar" may be present in normal amounts due to the organisms' loss of its ability to destroy this in chronic cases.

Diagnosis. Diagnosis, as has already been intimated, is rather difficult to make early in the disease. The intermittent fever rigors and the enlargement of the spleen often create suspicions of malaria. The rash in addition to the fever and splenic enlargement may suggest typhoid. If the joint involvement is at all prominent, acute articular rheumatism may be simulated. Brill's disease and subacute bacterial endocarditis (*Endocarditis lenta*) must frequently be considered. Gonorrheal sepsis usually occurs within a few months of an acute attack. Bacteriologic differentiation here helps. In typical cases with headache, fever of somewhat intermittent type, joint pains and the tender small erythematous nodular skin lesion, the diagnosis of chronic meningococcus septicemia may be entertained even in the absence of a positive blood culture. However, for definite and convincing diagnosis, a positive blood culture should be obtained. Meningococci grown from other places than the blood such as the cerebrospinal fluid, joint effusions, sinus washings, empyema aspirations, may settle any existing doubts. The presence of meningitis at any time during the disease is highly suggestive. Also the incidence of a number of cases of meningococcus meningitis may hint at the proper diagnosis.⁶

Course. The average duration of chronic meningococcus septicemia is several months. Vignot's 5 cases for example, lasted 85, 65, 69, 113 and 130 days. During a large part of this time the patient's condition may remain strikingly unchanged. Occasionally

there may be periods of comparative well-being when for some few days the patient is symptomless and even out of bed. On the other hand, the onset of meningitis causes an abrupt change in the clinical picture. Meningitis is nearly always a late manifestation when it does occur. Its appearance was noted on: 15 to 20 and 25th day in Netter's cases; 26 to 37 to 70th day in Pierre Louis Marie's cases; 28 and 40th day in Jottrain's cases; 60th day in Soloman's cases; 56th day in Morgan's case; and the 95th day in case of Moriquard, Bertaye and Charleux.

Does the complication meningitis make the outlook more serious? The seemingly apparent answer is not borne out by the reports. Cholier, Giroud and More analyzing this point state that cases without meningitis had a 50 per cent mortality, four deaths in 8 cases of their series, while those cases with meningitis had but a 33 per cent mortality—3 deaths in 9 cases. They believe that the localization in the meninges is favorable and helps the body to rid itself of the general infection.

Prognosis. The prognosis in chronic meningococcus septicemia is not always bad. Indeed, Sergent considers méningococcemia, not of the acute type, the most benign of the septicemias and from his observation resulted in 90 per cent cures. In other series mortality ranged from 10 to 50 per cent. Poor prognostic signs are: abundance of eruption, hyperthermia, profuse diarrhea, tachycardia and especially a positive blood culture with many colonies per cubic centimeters.

Treatment. No detailed routine treatment for this form of meningococcus infection has been established. However, it is thought that antimeningococcus serum should be given and by the intravenous route. Netter has obtained cessation of fever in 3 cases after 3, 4 and 6 injections. Vignot reported good results on 40 cc. daily. Stirpe obtained a cure with 180 cc. Contrary results are those of Neergaard who, finding no apparent improvement in the patient after the administration of 477 cc. of serum, discarded its use—the patient recovered. In our case, 307 cc. of antimeningococcus serum (polyvalent) were injected. Of this some was a specially concentrated solution made by the New York City Board of Health Laboratories. This serum was given intravenously and intraspinally and intramuscularly but without success. The series is too small to warrant any conclusions.

A strain or species specific antimeningococcus serum is preferable, if it can be obtained readily. However, if the type of meningococcus cannot be determined, the polyvalent antimeningococcus serum in 20 to 40 cc. doses by the intravenous route, given every twelve hours according to the severity of the patient's condition, is probably the best treatment. To assure oneself that the serum to be used is of value, agglutination tests should be performed between the serum to be used and culture of the meningococcus obtained from the patient.

Transfusions, nonspecific protein shock therapy and intravenous injection of colloidal metals all have been used with but little benefit. Fixation abscess and vaccine treatment have been favorably reported on.

Summary. Chronic meningococcus septicemia (chronic meningococcemia) was first described in 1902. Its rarity* is possibly more apparent than real (Marie). Scant notice given to this condition is in part due to the title "Epidemic Cerebrospinal Meningitis," which tends to direct all concern to the meninges and ordinary form of meningococcus meningitis.

Chronic meningococcemia is characterized by a rather sudden onset with headache, intermittent fever, joint symptoms, a typical erythematous skin eruption. There is little prostration and the course is long, lasting two to three months. The outcome is usually more favorable than in other septicemias. Meningitis is absent in a large number of cases. When it does occur it comes on late in the illness and apparently does not unfavorably influence the outcome. Other complications are considered. Early diagnosis is difficult, especially because the blood culture is frequently sterile until late in the disease. The treatment is with specific serum. A case is reported.

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* Since this paper was sent for publication, 2 cases of chronic meningococcemia were reported. A case reported by F. W. Marlow, Jr. (J. Am. Med. Assn., 1929, 92, 619) and 1 case the thirteenth, reported in this country, by Graves, Dulaney and Michelson (J. Am. Med. Assn., 1929, 92, 1922).

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GONORRHEAL ENDOCARDITIS WITH RECOVERY. A CASE REPORT.

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RELATIVELY few cases of proven gonorrheal endocarditis with recovery are recorded. In view of this fact, it seems worthwhile to report the following case. The case represents one in which the diagnosis of gonorrheal endocarditis seems certain. In addition to the unusual feature of recovery, the case is of interest as to the location of valve damage, and concerning the embolic manifestations which occurred. Furthermore, while recovery may have been purely accidental, the case may be of interest from the angle of therapy.

Report of Case. M. L., aged twenty-two years, a clerk by occupation, single male, was first seen on February 17, 1928. At this time, the patient had a slight elevation of temperature and he stated that he had been having fever for about a week. He, however, had not been confined to his bed during this time, and he had had no chills. He had had no evidence of rheumatic involvement. He complained only of fever and prostration. His past history was negative, except for a urethral discharge that had been present since early in November of 1927. This urethral discharge had not been recognized as gonorrhea until February 17, 1928, when positive smears were obtained. One year previous to the present illness the patient

had passed an insurance examination in which no cardiac abnormality was noted.

The social history was negative except for the excessive use of cigarettes. The physical examination, at the time he was first seen, was negative except for a slight fever (99.6°) and a thick, yellowish urethral discharge. There was no prostatic enlargement or tenderness and no tenderness over either kidney. There was no evidence of epididymitis. The red blood cell count was 4,160,000, the hemoglobin 77 per cent (Dare), the white blood cell count 11,800. The differential count gave the following figures: large lymphocytes, 24 per cent; endotheliocytes, 1 per cent; large mononuclear cells, 2 per cent; polymorphonuclear cells, 71 per cent; mast cells, 2 per cent. The urine showed a trace of albumin and many pus cells. It was otherwise negative.

The course of the illness may best be presented by recording the daily notes which were made.

February 24, 1929. The patient has had, since first seen, an irregular elevation of temperature and acceleration of pulse rate. He had today, for the first time, a severe chill and, following the chill, a temperature of 105.6° .

February 29, 1929. Routine physical examination is negative except in the following findings concerning the heart. The heart is beating rapidly and out of proportion to the temperature (temperature, 99.6° ; pulse, 104). The apex beat is slightly displaced to the left in the fifth interspace, and on percussion one notes slight left-sided widening of the area of cardiac dullness. On auscultation, there is heard in the pulmonary area, a soft, low-pitched systolic murmur. This murmur is heard over a very limited area and is a very slight one. The pulmonic closing sound is split, accentuated and harsh. All other valve sounds are clear. No petechiæ are noted.

Comment. The history of acute gonorrhea followed by a febrile course, with a chill and pulse out of proportion to the temperature, occurring after local symptoms have largely disappeared, and in the presence of a low-grade leukocytosis, and the appearance of a murmur in the pulmonary area suggests gonorrheal endocarditis with probable involvement of the aortic or pulmonary valve. The blood pressure is 105 systolic and 65 diastolic.

March 1, 1928. The patient is essentially the same as yesterday. There is a distinct systolic murmur in the pulmonary area. The murmur is a little louder than when last noted.

March 2, 1928. Auscultation of the heart today reveals a very slight, but definite, early diastolic murmur in the pulmonary area. This is the first time that a diastolic murmur has been heard. The systolic murmur has disappeared.

March 3, 1928. The patient had at 10 A. M. today a severe chill. Before this chill his temperature was 99° , his pulse 89. Following the chill his temperature went up to 104° and his pulse to 130. Four hours later the temperature dropped back to essentially its former level. Of late the patient has had frequent, drenching night sweats.

March 7, 1928. The patient had another chill today (5.30 A.M.), but this chill was not followed by the sharp temperature rise previously recorded. The temperature for the past four days has ranged around 101.5° to 102° in the afternoons, dropping in the forenoons to 99° to 100° . The pulse in general has been out of proportion to the temperature. Auscultation of the heart reveals the diastolic murmur previously recorded, best heard in the pulmonary area. It is a louder murmur and now occupies the whole of diastole. The area over which it may be heard is somewhat limited. It is transmitted a short distance down the left border of the sternum.

A positive blood culture, showing a pure growth of gonococci, is reported today. The culture was obtained on a bone-meat infusion agar and the

colonies appeared after four days' incubation. A number of blood cultures have been taken but all had until today been sterile. The blood from which this positive culture was obtained was secured immediately after a severe chill. This had not been true of the samples of blood previously obtained for culture. A vaccine is to be prepared from the culture obtained today.

March 8, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 9, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 11, 1928. The patient has been severely ill since the last note. He has had three chills with temperature rise to between 103° and 104° . A transfusion was given him immediately after his chill on March 8, 1928, and appeared to produce no reaction. The transfusion on the ninth was given about four hours after a chill. The pulse and temperature are, in general, proportionate now.

March 14, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 15, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 16, 1928. Since the last note the patient has been better. His temperature has not been above 100° . His pulse has been relatively quiet.

March 20, 1928. Examination of the heart shows the right border of cardiac dullness moderately displaced to the right. The diastolic murmur, best heard in the pulmonary area and transmitted down the left border of the sternum, is heard. The blood pressure is 110 systolic and 65 diastolic. No petechiae are present. It is believed that the valvular involvement is of the pulmonary valve.

March 22, 1928. The patient has been decidedly sicker. Beginning March 16, 1928, his temperature began to show wide excursions, varying 97° to 104° . On March 20 he had a severe chill with temperature rise to 104.3° and a pulse rise to 120. On March 21 his temperature went to 104.4° with his pulse to 135. He continues to have drenching sweats.

March 23, 1928. The patient is given today 150 cc. of serum from a donor who 3 months ago recovered from gonorrheal arthritis.

March 26, 1928. The patient is given today 250 cc. of citrated blood. He has had a low-grade polymorphonuclear leukocytosis from the onset of his illness. Repeated examinations have shown the white cells between 10,000 and 15,000. The patient has at no time shown much reduction in his red-cell count or in the percentage of his hemoglobin. Repeated examinations of the urine have failed to show blood. The urine does show a trace of albumin and occasional casts. Examination of the heart today shows a very striking, harsh, diastolic murmur, best heard in the pulmonary area and transmitted down the left border of the sternum. No murmurs are heard in other valve areas. The blood pressure is 110 systolic and 68 diastolic. There are no peripheral evidences of aortic regurgitation.

March 27, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 30, 1928. Yesterday at 1.30 p.m., the patient, while feeling quite comfortable, suddenly developed a severe, knifelike pain in the left lower axillary region, making breathing very shallowly and he grunts with each respiration. There is impairment to percussion in the left lower thorax, laterally and posteriorly. Over this area breath sounds are diminished and voice transmission is diminished. The abdomen is markedly bloated with gas. The patient coughs with difficulty and brings up blood-stained material. Immediately following the appearance of the above pain he was profoundly shocked.

April 2, 1928. The patient received today 0.2 cc. of autogenous gonococcus vaccine of a strength of 400,000,000 per cc.

April 4, 1928. A blood transfusion of 250 cc. of citrated blood is given. The small dose of vaccine created no reaction.

April 5, 1928. A blood transfusion of 250 cc. of citrated blood is given. The patient has been running a much lower level of temperature, this since

March 25, 1928. Examination of the heart shows the murmur heretofore described. At present the percussion outline of the heart seems essentially normal. There is possibly slight right-sided widening. The painful condition of the lung has gradually cleared and at present the patient is quite comfortable. There is slight impairment to percussion over the left base with diminution of breath sounds over the area of impairment.

April 10, 1928. A blood transfusion of 250 cc. of citrated blood is given, 0.4 cc. of the above-mentioned vaccine is also given.

April 11, 1928. The injection of the vaccine yesterday was followed by a drop of temperature from 98.6° to 97.5° and followed by a rise of temperature to 101° . The patient experienced a rather severe reaction to the vaccine. The patient's temperature today reached 103.2° , the highest point for the past four days.

April 12, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 14, 1928. One-half cubic centimeter of the autogenous vaccine today was followed by a severe reaction. To date no appreciable change in the general course of the case has appeared. In view of this, and in view of the patient's dread of the reaction produced by the vaccine, it is thought wise to discontinue its use. The patient developed suddenly today pain in the left upper chest, made worse by deep breathing. This involved the scapular area and pain extended into the neck. The patient was not disturbed for an examination of his chest. He is coughing blood-stained mucus. He appears to have had another pulmonary embolism.

April 16, 1928. The patient's general condition remains the same. His temperature ranges from 99° to 102° . The condition of his heart is essentially the same.

April 18, 1928. The painful condition of the chest gradually disappeared following the occurrence of April 14, 1928. Again today, however, he complains of severe pain in the left upper thorax, and he is again coughing blood. This is taken to be the third pulmonary embolism which has occurred.

April 19, 1928. One very satisfactory feature in connection with the care of this patient is the fact that he has eaten well during practically all of his illness. He has not lost very decidedly in weight. Another feature which bears mentioning is the fact that he has smoked very heavily of cigarettes during the whole course, consuming from 20 to 30 cigarettes a day. He is clinically better, at present.

April 20, 1928. The pain above mentioned has continued to date. It is of a pleural type and has required morphin for relief.

April 23, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 24, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 28, 1928. Since the last note the patient has been strikingly better. His temperature has been essentially normal. His pulse in general has been quiet. He is eating well, sleeping well and digesting well.

The diastolic murmur, which seems to originate in the pulmonary valve, is as previously recorded. At no time during the course of the case has there been the blood pressure of an aortic regurgitation. At no time has there been evidence of congestive failure.

April 29, 1928. The patient again has had a pulmonary embolism, characterized by severe pleural pain involving the left base posteriorly. Following the pain he had a violent chill. His temperature, which had been essentially normal so long, went to 103° , and his pulse to 140. The patient became cyanotic, and he again coughed blood. His condition was so bad that he was not disturbed for examination of his chest, the clinical picture being so strikingly that of an embolism.

May 2, 1928. The patient has had, since the last note, a "steeple" chart. His temperature reached 103° today, his pulse 120.

May 7, 1928. A blood transfusion of 250 cc. of citrated blood is given.

May 8, 1928. A blood transfusion of 250 cc. of citrated blood is given.

May 10, 1928. Following the last embolic manifestation, the patient gradually improved and he now has a normal temperature. His pulse varies between 80 and 100. He is clinically in good condition, at present. The heart murmur remains essentially unchanged. There is very little, if any, right-sided widening and no left-sided widening is apparent on percussion. The blood pressure is 115 systolic and 70 diastolic.

May 30, 1928. The patient is discharged. He has consistently maintained a normal temperature since the last note. His pulse has varied somewhat, but has ranged around 80 beats per minute. He has continued to gain in weight and strength. He has been gradually allowed to sit up during the past week. Final examination of the heart is as last recorded. Examination of the lungs reveals some impairment to percussion over the left base and lower axillary region, with diminution in intensity of breath sounds and of transmitted voice.

August 3, 1928. The patient reports that he is well. He has not attempted strenuous work, but experiences no cardiac difficulty on ordinary exertion.

July 12, 1929. The patient reports by letter that he is well.

Epicrisis. In all, fourteen blood transfusions were employed. All transfusions were of 250 cc. of citrated blood. In giving the transfusions the donor was bled 500 cc. and one-half this amount was given, the other half being kept in the icebox and given the following day. No reactions to the transfusions occurred. One injection of 150 cc. of convalescent serum was given.

A limited use of autogenous vaccine appeared to be of harmful effect.

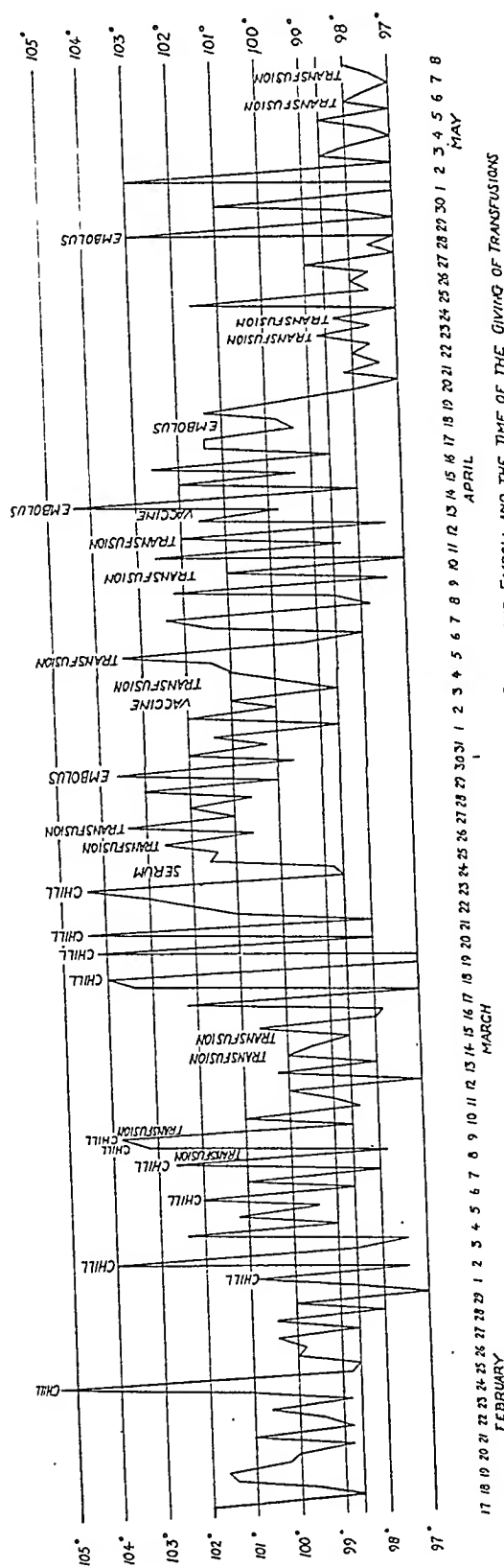
A liberal food intake was maintained throughout the illness. Drug therapy, as indicated for pain and sleep and for bowel elimination, was employed.

A moderate leukocytosis was present throughout the illness. The highest of 20 counts was 15,900, the lowest 9100. In all counts there was a moderate increase in the percentage of polymorphonuclear cells. A marked anemia did not occur. With the numerous transfusions the figures for the red-cell counts and hemoglobin determinations were near normal, throughout the entire course of the case.

Frequent examinations of the urine were made, and commonly a trace of albumin and a few casts were present. Pus, which had been present when the patient was first seen, soon disappeared. The urine at no time showed red blood cells.

The location of the basal murmur, the occurrence of numerous pulmonary emboli, and the absence at all times of the blood-pressure change of aortic insufficiency make the location of the valve damage certainly the pulmonary valve. The patient now represents a true case of acquired pulmonary valvular disease.

A chart showing the high and low temperatures of each day follows.



Summary. 1. A case of gonorrheal endocarditis with recovery is reported.

2. The findings making certain the diagnosis are recorded.

3. The localization of the disease process in the pulmonary valve is shown and the reasons for this localization are given.

4. Treatment of the case is reviewed and emphasis placed on the apparent value of frequent small blood transfusions in this treatment.

AURICULAR FLUTTER FOLLOWING DIRECT INJURY TO THE CHEST.

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THE effects of direct injury to the chest have, in recent years, been recorded in a number of contributions to the literature. Various types of heart conditions have been described resulting from external violence. The exact pathogenesis of these conditions remains, however, speculative in certain types of cases.

The literature is very scant concerning instances of auricular disturbances that follow direct violence to the chest. What the pathologic changes are that produce this condition one cannot declare with certainty. However, the possibility of subepicardial ecchymosis in the auricular muscle must be considered. The cardiac damage in these cases is not disputable.

Levinson¹ and Kahn² have each reported a case of auricular fibrillation that resulted from a blow to the anterior chest wall. Rosenson³ has described a case of transient heart block produced by a blow. More serious lesions have been described extensively in the literature. Recently, the author has reviewed the subject at some length.

In the present communication, I desire to present a case of unusual interest, as it is the first on record of auricular flutter produced by injury to the chest wall.

Case Report. John M., a robust porter, aged fifty-nine years, gave a negative family history. His wife and three children were well; there had been no miscarriages and no history of familial diseases. He had suffered from occasional tonsillitis years ago, and at that time had some stiffness of the joints. Ten or fifteen years before the present illness, he was injured in the left chest by a falling barrel, fracturing some ribs.

The history of the accident is as follows:

On March 11, 1929 at 12.30 p.m., while holding down and leaning over the handle of a crowbar which was forced under a heavy soda fountain,

the handle recoiled, striking the patient twice sharply against the lower left breast region. He screamed out loud with pain, was momentarily dazed and stepped away releasing his hold. He did not fall down, did not faint or become unconscious; did not vomit, and did not cough or expectorate blood.

The sharp pain continued and was localized outside of, and below, the left breast region, but it did not prevent the patient from continuing his regular work that day. In the evening, he applied chloroform liniment, but could not sleep for the pain. He did light work on the day after the accident, and on the following day he was sent by his employer to a physician, who applied adhesive strips to immobilize the left chest. The patient continued work for two days more and then, on returning home, he suddenly fell and almost fainted. That night, he could not sleep because of precordial pain. He has not been able to work since then, but has visited his physician almost daily for "baking" treatment of the left chest.

On March 20, Roentgen ray of the chest revealed old fractures of the eighth and ninth left ribs.

At the time of my examination about three weeks after the injury, the patient complained of weakness, precordial pain, palpitation, and shortness of breath. This was worse on exertion, but also occasionally occurred while at rest. At night, he found difficulty in breathing and had "to sit up for pain." There was occasional dizziness, but no headache; moderate cough and expectoration, but no hemoptysis. There was moderate edema of the legs. Vision and hearing had become somewhat defective.

The physical findings three weeks after the accident were as follows: The eyes, mouth, nose and glands revealed nothing of significance. There was a bilateral chronic catarrhal otitis media with considerable deafness. The skin showed a desquamation in the left axilla with erythema due to physiotherapy. There was a scar of an old carbuncle across the back of the neck.

The right border of the heart percussed 3 cm. from the median line; and the left border 11 cm. from the median line, at the nipple line. The apex beat was felt poorly, diffuse in the fifth space within the nipple line. The heart action was irregular in phases, with occasional extrasystoles. The first sound at the apex was clear and of fair muscular quality. No murmurs were audible. The second aortic sound was slightly accentuated. There was moderate temporal tortuosity and a Sahli capillary zone around the lower chest. The blood pressure was 160 systolic and 100 diastolic, with an alternating pressure of 130 systolic and 100 diastolic, every other beat.

The chest was somewhat asymmetrical with lateral flattening in the left axilla. Expansion was fair and equal. There was some diffuse tenderness over the left lower axilla, more marked over the seventh and eighth ribs in the midaxillary line. There were no palpable fractures, crepitus or deformity. There was no swelling, ecchymosis, or other external evidence of injury. There was moderate supraclavicular retraction.

The lungs gave a hyperresonant note on both sides, anteriorly. Breath sounds were vesicular, and there were atelectatic râles present, which were more marked at the right base posteriorly.

Liver dullness extended from the sixth rib to below the free border, the edge was not distinctly palpable. The abdomen revealed no masses or tenderness. There was a large, right, oblique inguinal hernia protruding into the scrotum. The left inguinal ring admitted the finger tip, but there was no hernia.

Orthopedic examination showed slight scoliosis with convexity to the right. The patient had difficulty in lying down and sitting up because of pain in the left axilla. There was some pain on full extension of the knees. He walked with a gait favoring his left side. The upper extremities showed

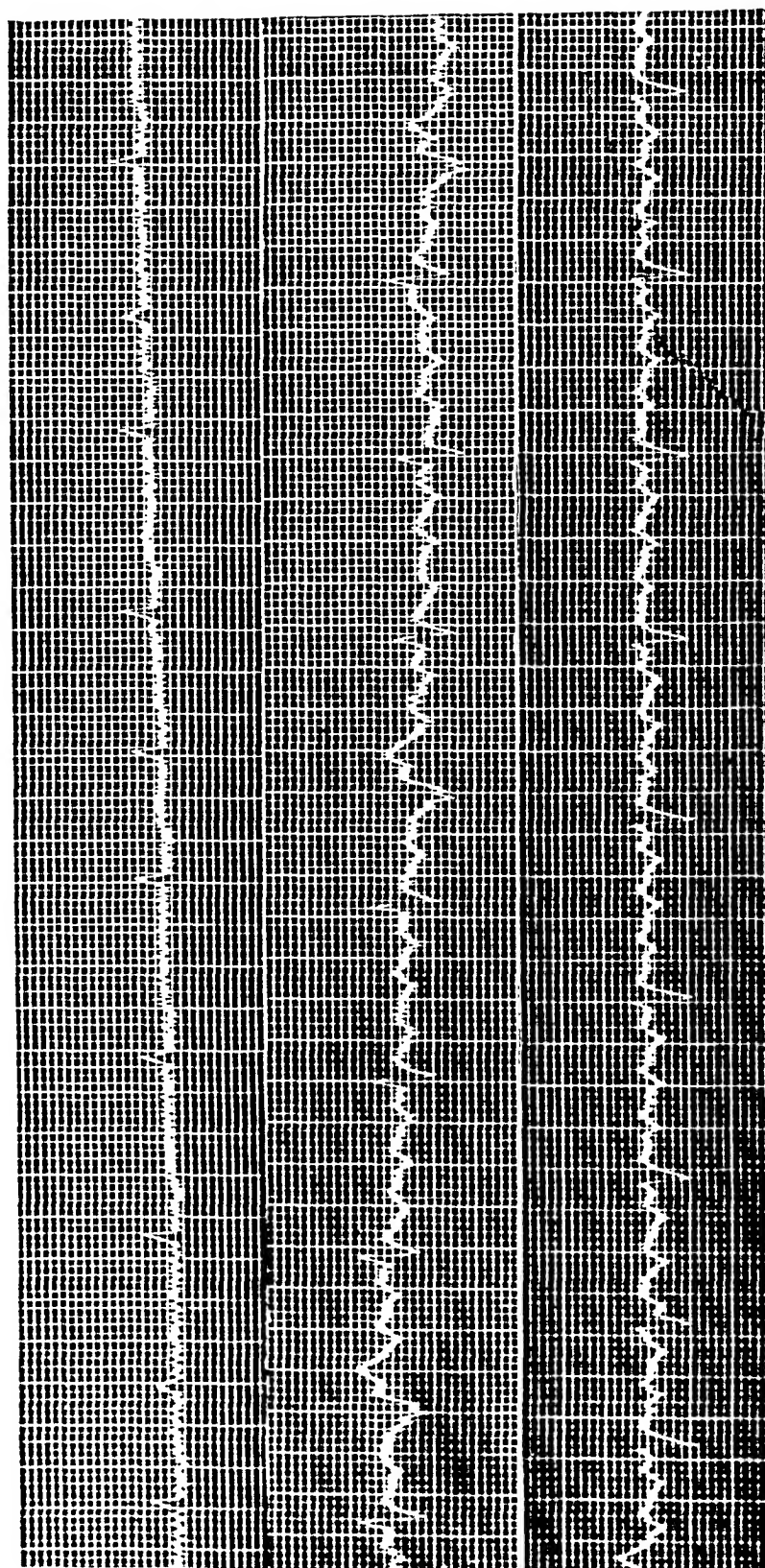


FIG. 1.—Electrocardiographic tracings taken three weeks after the injury to the chest, showing auricular flutter and occasional ventricular premature beats.

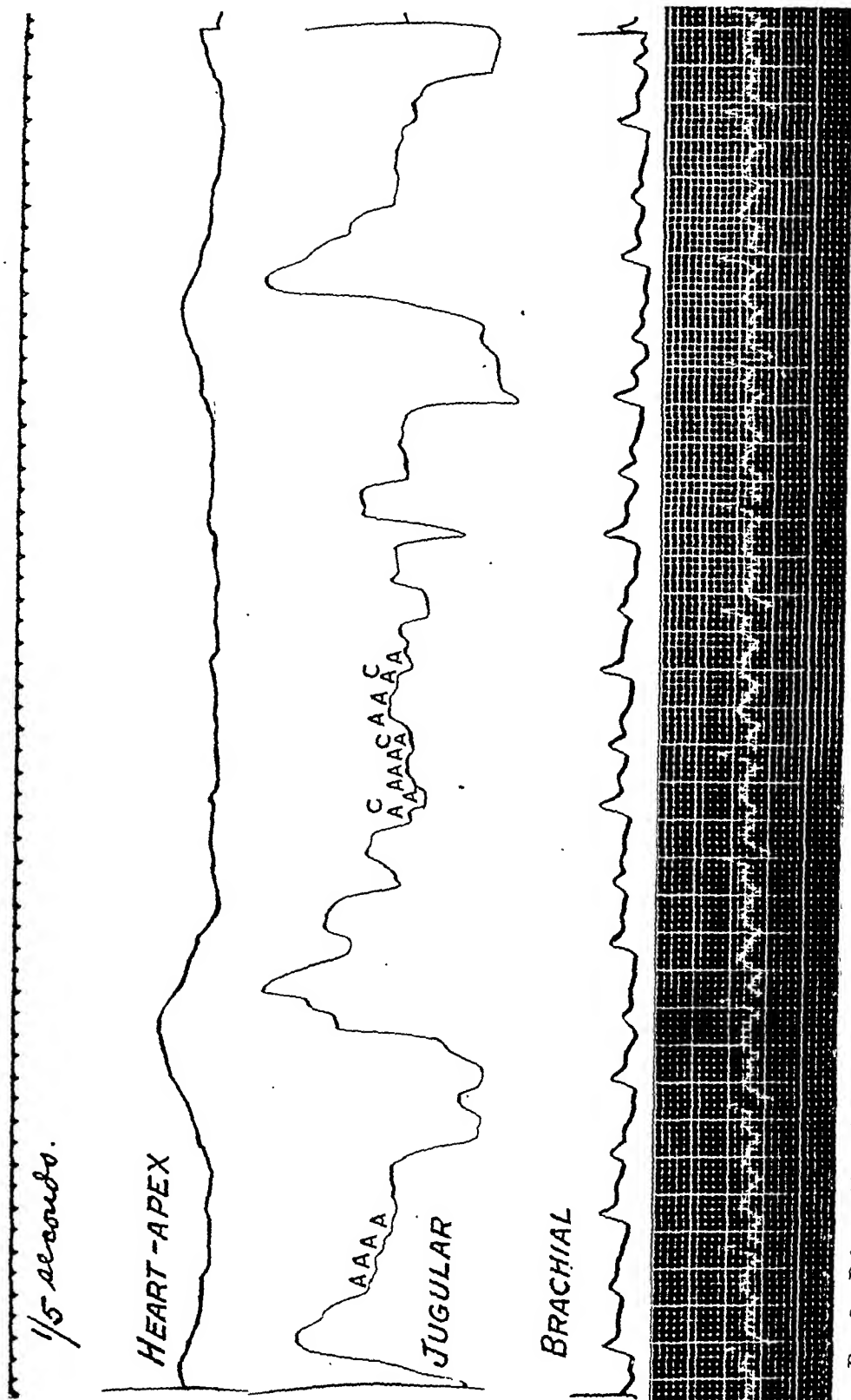


FIG. 2.—Polygraphic and electrocardiographic tracings (Lead II) taken three weeks after the injury to the chest, showing auricular flutter with a rate of 3 to 1 and 4 to 1 in alternating cycles. The jugular curve presents the auricular waves and the brachial tracing shows the alternating amplitude of the waves.

old swelling with Heberden nodosities about the finger joints. There was marked swelling of the lower extremities up to the level of the knees. The tendon reflexes were normal.

The urine showed some albumin, but no casts microscopically. The blood Wassermann test was negative.

Teleroentgenographic examination of the heart and aorta revealed the following: The patient was of hypersthenic habitus. The heart was obliquely oval in shape, and there was increased obliquity of the cardiac axis. It was enlarged in its transverse and longitudinal diameters, and the right auricular and left ventricular curves were accentuated. The aortic arch was sclerosed. The measurements were as follows: Median right, 9 cm.; median left, 9.5 cm.; aorta, 7 cm.; longitudinal, 18 cm.; pulmonary fields, 27 cm.

The polygraphic tracings showed the existence of bigeminy over long periods in which every alternate cycle was extrasystolic followed by a compensatory pause. At other times these extrasystoles were infrequent and a regular pulse was maintained at a somewhat slow rate. The jugular curve showed very characteristically the waves of auricular flutter. The apex tracing was small and trapezoidal.

The electrocardiogram showed left ventricular preponderance. There was an inconstant ventricular rate of about 75 to 80 per minute. The auricular rate was 300 per minute with distinct waves of auricular flutter shown conspicuously in Leads II and III. There was a relative heart block of 4 to 1. At times, the ventricular rate increased over a short period, with a relative 2 to 1 block. There were occasional aberrant waves of conduction through the ventricle with slight distortion of the ventricular cycle. Occasional premature beats occurred, arising from the apex of the right ventricle. During some periods in the electrocardiogram, there was present a 4 to 1 and 2 to 1 alternate relative auriculoventricular block, producing an alternans type of pulse due to the difference in ventricular filling at every other cycle.

The voltage was low in all three leads. There was no widening of the *Q-R-S* wave, and no evidence of myoneural conduction defect.

A month later, the liver was found to be enlarged to four fingers below the costal margin. The edema of the extremities persisted.

The Roentgen ray shadow at this time, showed a slightly increased transverse diameter of the heart, but the occasional ventricular premature beats and the auricular flutter persisted in the electrocardiogram.

Treatment by digitalis and quinidin, and a strict Karrel diet was ineffectual in producing improvement of the patient's condition which grew progressively worse. Swelling of the scrotum developed and the urine showed an increased amount of albumin with a rare hyaline and numerous granular casts, and occasional red blood cells.

The condition persisted unimproved for another month.

The patient died four months after the accident. Unfortunately a postmortem examination was not made.

Discussion. In this case, the cardiac symptoms, including the sharp pain in the precordial region, followed immediately upon the recorded accident. In point of time the onset is therefore closely and directly associated with the injury. In the absence in the history and physical examination of any of the other causes which might induce auricular flutter, such as marked arteriosclerosis, syphilis, hypertension, rheumatism, Grave's disease or any other toxic or infectious conditions, we are led to the assumption that there

was a direct relationship between the alleged accident and the patient's condition.

His previous ability to do hard work certainly gainsays any existence of this condition prior to the alleged direct trauma to the chest. The location of the extrasystolic cycle is particularly suggestive of a relationship, as the right ventricle is most exposed to the effects of direct violence to the anterior chest wall. The pathologic changes that may have taken place from the injury are necessarily speculative. The possibility of subepicardial ecchymosis in the auricular muscle is to be considered. The process takes a long time to heal and therefore the auricular flutter may last an indefinite period of time.

There is an interesting feature suggested by the electrocardiogram that deserves a word of note. In Fig. 2, it is to be noted that the alternate ventricular cycles occur after every four and every two auricular contractions. This produces an arrhythmia which is hardly appreciable as one listens to the auscultatory effects in taking the blood-pressure measurements. The impression then is a distinct pulsus alternans with a difference of 30 mm. in the systolic pressure between alternate cycles. This difference is equivalent to half the pulse pressure. One may judge from this that the auricular function in this case in producing ventricular filling is a most important one. Apparently every contraction of the auricle during flutter contributes its definite measure of blood to the ventricular volume.

Another feature in the electrocardiogram is of great and suggestive interest. It is to be noted that preceding every ventricular cycle that follows two auricular contractions, there is a normal *P-R* interval of 0.2 seconds. When four auricular waves occur, conduction becomes reduced to 0.14 seconds. It is thus seen that there is an improvement of conductivity following the longer periods of block.

We shall have to leave unanswered the question of why in some cases auricular fibrillation occurs as a result of direct injury to the chest; and in this case, auricular flutter. It is possible that the incidence of this condition depends upon the location of the lesion in the auricular musculature, its proximity to the region of the sinus node, and its distribution otherwise throughout the auricular wall.

Whenever a colliding force has been directed against the precordial region of a patient, the possibility of myocardial damage must be kept in mind. If fracture of the ribs or injury to the pleura occurred such suspicion becomes emphasized. The presence of irregular action which supervenes upon violence to the heart is a significant sign. Although the pain has no particular characteristics, it is usually localized over the injured area and sometimes radiates to the left axilla or below the left breast.

It must emphatically be recognized that milder injuries of the

myocardium, consistent with life over a varying length of time, may take place. The symptoms and signs, as well as the disability in such cases, usually persists.

Summary. 1. A case is reported in which, following direct violence to the chest, auricular flutter was discovered with signs of heart failure.

2. The pathogenesis of this condition is only to be surmised. The possibility of subepicardial ecchymosis in the auricular muscle is to be considered.

3. Milder injuries of the myocardium may result from direct violence to the chest with consequent disability, although consistent with continued life.

4. The blood pressure findings suggest that a definite amount of ventricular filling is produced by each auricular contraction.

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THROMBOSIS OF THE HEPATIC ARTERY.

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THROMBOSIS of the hepatic artery is a pathologic curiosity and has been reported only once before by Lancereaux.¹ Rolleston² suggests that this case might have been due to an embolism from thrombi in the vessels of the lower extremities. Embolism of this vessel is also rare but cases have been reported by Chiari³ and others. Chiari found complete necrosis of the liver, the main trunk of the vessel being involved. Lancereaux⁴ and Ogle⁵ have reported cases of embolism at the bifurcation. In Ogle's case there were anemic infarcts in the liver but no general necrosis. Septic embolism of the smaller branches of the hepatic artery occurs in hemic infections and gives rise to pyemic abscesses. Embolism occurs in generalized tuberculosis and sarcomatosis (Rolleston²). Closure of the smaller vessels is usually not followed by necrosis (Kaufmann⁶).

Friedenwald and Tannenbaum⁷ recorded 65 cases of aneurysm of the hepatic artery. In 5 of these cases, the aneurysmal sacs contained thrombi (Leduc, Riedel, Reichman, Tuffier and Hogler). Three others showed thrombosis of hepatic artery as well as the sacs (Liverato, Teacher and Jack, Merkel). Three showed necrotic areas in the liver (Brion, Bode, Dean and Falconer). In a case of

a small tuberculous aneurysm of a branch of the hepatic artery associated with thrombosis of the portal vein, Thompson⁸ found definite infarcts in the liver. Stokes and Inglis⁹ reported an aneurysm of the hepatic artery with acute pneumococcic endocarditis raising the question of the infectious nature of this aneurysm.

In this paper, the metabolic changes are not discussed, as they are not brought out in the two cases here reported. These are presented; one from the Laboratory Division of Montefiore Hospital under the supervision of Dr. David Marine, and the second from the Krankenhaus im Friedrichshain, Berlin, through the courtesy of Prof. Ludwig Pick.

Case Reports. CASE I.—M. L., male, aged forty-three years, born in Russia, resident of U. S. A. seventeen years, an operator, was admitted to hospital, June 11, 1927. He died June 20, 1927. C. C. Dyspnea. Pain in stumps of both legs. Loss of 40 pounds in one year.

Present Illness. Patient had cramplike pains in both legs in 1915, worse on walking, relieved by resting or sitting. In 1916, amputation of the right leg above the knee was performed on account of the development of gangrene of the first and fifth toes. In November, 1921, amputation of the left leg below the knee was performed at the Lebanon Hospital for gangrene of the first toe. The popliteal artery was almost completely obliterated by a fibrotic canalized thrombus with an inflammatory reaction in the coats of the vessel. The diagnosis was thromboangiitis obliterans. Four further operations to upper third of left thigh were performed on account of failure of the stump to heal; last in December, 1926. Pain recurred in both stumps.

In May, 1926, he developed sudden onset of shortness of breath, fear of impending death, choking sensations and pressing pain over the precordium radiating to sternum and up to neck. He was rushed to a hospital where he remained three weeks. He was given digitalis and felt relieved. He spent varying short periods in four institutions for recurrent heart attacks which became more frequent, sometimes two or three in twenty-four hours. On two occasions he expectorated bright-red blood. He had spots before his eyes and diplopia. For two months he had edema of the stumps, constipation, piles, indigestion, nocturia two to three times, urinating three to five times daily. In May, 1927, he had bloody urine for four days. Previous and family history were irrelevant.

PHYSICAL EXAMINATION. Sallow complexion with marked pulsations of the vessels of the neck, anxious expression, orthopnea, marked dyspnea, wasting.

Head. Complete alopecia, pupils somewhat irregular, react somewhat sluggishly to light, well to accommodation. Two artificial teeth, numerous gold crowns, tongue slightly coated, pharynx slightly reddened.

Neck. Right submaxillary gland enlarged, thyroid slightly enlarged.

Chest. Negative.

Lungs. Dullness to flatness with slightly diminished breath sounds, D8 to D10, left posteriorly; small moist râles at both bases.

Heart. Apex in sixth interspace at anterior axillary line, rate 98, no thrill, no enlargement to right; dullness in fifth interspace, 10.5; sixth, 11.2; occasional premature beat, soft low, systolic murmur is heard best in the third interspace to the left of the sternum. A2 is more accentuated than P2. Radial artery is beaded, pulses forceful, blood pressure: right arm, 182 systolic and 118 diastolic; left arm, 190 systolic and 120 diastolic.

Abdomen. Liver four and one-half fingers-breadth below the costal margin; fluid wave, free fluid in flanks.

Genitalia. Attached to the left spermatic cord, a hard egg-shaped, tender mass is palpable.

Extremities. Slight tremor of the fingers; both legs amputated, right stump at junction of middle and lower thirds of thigh, left at junction of upper and middle thirds; both markedly edematous.

Course. June 19, 1927. The patient suddenly became cyanotic, dyspneic, respirations 32 per minute, complained of cardiac pain and abdominal distention. The pulse was strong and regular. Edema of hands rapidly developed, loud moist râles were present at both bases with fluid in the left chest and ascites. Respirations were 56 per minute. Blood pressure rose to 232 systolic and 130 diastolic. Patient received morphin and atropin. He became markedly cyanotic, stuporous, irrational, respirations were labored. He died at 3 A.M., June 20, 1927.

Laboratory Findings. Red blood cells, 5,400,000; hemoglobin, 92 per cent; white blood cells, 8120; polymorphonuclears, 82 per cent; small lymphocytes, 14 per cent; large lymphocytes, 4 per cent; blood sugar,* 172; blood urea, 19.1; blood Wassermann, negative. Urine: trace of albumin; P.S.P.: 8 + 10 per cent = 18 per cent.

Electrocardiogram. L-V-P. P notched in first and second leads; slight peaked notching of Q-R-S in second lead; A-V conduction time -0.18.

Roentgen Ray. Fluid at right base; heart enlarged to left.

Temperature. 98.6°, on admission, to 96.6° before death.

Anatomical Diagnosis. Thromboangiitis (clinical); generalized atherosclerosis, moderate; cardiac hypertrophy and dilatation; surgical amputation lower extremities; *thrombosis of hepatic artery*; thrombosis of left iliac artery; arteriolo- and arteriosclerosis of kidneys; adenoma suprarenal; hydrocele spermatic cord (left); terminal bronchopneumonia.

General appearance and external findings were similar to physical findings. Liver was 2 cm. below the costal margin. Abdomen contained a liter of turbid fluid. There were adhesions between fundus of gall bladder and hepatic flexure of colon. The intestinal coils were moderately distended. Stomach was markedly dilated.

Heart. Weighed 550 gm. *Measurements:* Aortic ring, 7 cm.; mitral ring, 10; pulmonic ring, 8.5; tricuspid ring, 12; left ventricular wall, 15 mm.; right ventricular wall 5.8 mm. Heart was markedly enlarged, right side flabby, left ventricle firm. Epicardial surface was thickened, opaque in a small area over the left auricle. Sinuses behind the pulmonic leaflets were markedly dilated and thinned out. There was marked dilatation and slight hypertrophy of the right auricle and ventricle, especially in the region of the pulmonary conus. Left auricle was slightly dilated, endocardium moderately thickened, opaque. Left ventricle was markedly enlarged, firm marked dilatation, moderate hypertrophy. Endocardium showed a few scattered yellowish-white puckering, up to 1 cm. in diameter. Myocardium was firm, pale.

Lungs. Right: All three lobes were voluminous, upper two lobes were soggy. Lower lobes contained scattered irregular nodules of consolidation. On section, there was marked chronic passive congestion throughout with slight edema. In lower lobe scattered areas of early bronchopneumonic consolidation were present. The bronchi were dilated and contained large amounts of mucopurulent material, mucous membrane was purplish. Vessels: All arteries were moderately thickened with numerous atheromatous plaques. Root glands were edematous, enlarged, moderately congested.

* One year before (June 15, 1926, Lebanon Hospital), blood sugar, 104; urea, 20 and Wassermann negative.

Pancreas. Organ was small. On section, there was moderate fatty and fibrous replacement of acinous tissue, islands were small.

Pelvic Organs. The *bladder*, *prostate* and *seminal vesicles* were negative. *Testes:* There was a hydrocele of the left cord, represented by a thick-walled cystic structure filled with fluid. The cyst measured 3 by 2 cm. The *epididymes* were negative.

Vessels. Aorta: From the root to the bifurcation there was a diffuse atheromatous involvement showing in places large elevations of translucent watery tissue. Throughout there were parallel linear streaks suggestive of lues. The branches showed similar thickening and parallel puckering. In the terminal portion of the iliac and the proximal portion of the femoral arteries there was a breaking down occluding thrombus. There were no thrombi in the right iliac artery. The *vena cava* and *tributaries* were negative.

MICROSCOPIC NOTES. Heart. Moderate fatty infiltration of muscle fibers.

Lung. Several sections show moderate chronic passive congestion, very slight thickening of intima of smaller vessels and marked thickening of the intima of the larger vessels. In one section, a small vessel shows almost complete obliteration. One section shows a large area of recent bronchopneumonia.

Liver. Marked passive congestion with slight degeneration at center of lobules. A large artery is markedly thickened due to proliferation of intima. Sudan III stain shows moderate fatty changes in liver cells. Glycogen stain negative.

Spleen. Marked passive congestion, Malpighian bodies are of average size, vessels are moderately thickened and hyalinized.

Kidneys. Several sections show a moderate number of glomeruli partially and completely obliterated by hyalinized fibrotic tissue, moderate number of tubules distended and filled with pink-staining homogeneous substance; marked congestion; marked thickening of the intima of the larger and smaller vessels with almost complete obliteration of the lumen in places. Marked small round-cell infiltration throughout and in pelvis.

Suprarenal. Marked congestion. Cortical cells pale-staining and contain abundant lipoid. Another section shows a large cortical adenoma 1 by 0.5 cm. in the gross. Vessels show moderate thickening of the intima.

Pancreas. Two sections: Two small vessels in one section show complete obliteration of lumen with recanalized thrombi. Both sections show marked fatty replacement of acinar tissue. Islands average. Marked thickening of intima of vessels.

Prostate. Average. Marked thickening of the intima of the larger vessels.

Testis. Atrophy of tubular elements. Vessels show moderate thickening of intima of vessels.

Spermatic Cord. Marked thickening of the intima of the vessels, two of them are partially occluded by organized thrombi. On the free surface, there is a layer of organized granulation tissue.

Thymus. Well involuted.

Stomach. Slight catarrhal inflammatory reaction of mucous membrane.

Colon. Marked congestion.

Lymph Nodes. Moderate involution.

Aorta. Four sections: Hyalinization and fibrous thickening of intima with areas of cholesterol crystal spaces in several sections, with slight perivascular small round-cell infiltration.

Vessels. For pictures and schematic representation see figures and Chart II. *Iliac artery:* Marked thickening of the intima with hyalinization and fibrosis. Unclothed blood in lumen. *Aorta:* Moderate athero-

sclerosis. *Hepatic artery*: Marked atherosclerosis, bland laminated clot. *Left branch*: Slight atherosclerosis, lumen is filled with bland laminated clot and small amounts of blood. *Right branch*: Occluding organized thrombosis.

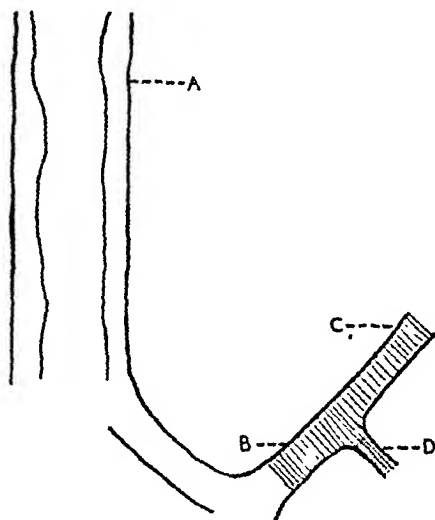


CHART II.—Schematic diagram of hepatic artery and branches. A, aorta, moderate atherosclerosis; B, main artery, marked atherosclerosis, bland laminated clot; C, left branch, slight atherosclerosis, bland clot; D, right branch, occluding organized thrombus.

CASE II.—(Städtisches Krankenhaus im Friedrichshain.) A female, aged fifty-four years, was admitted to Ward 15A of the hospital, July 24, 1928, in a moribund condition and died two hours later; on admission, temperature 38° C., pulse 93. History was not obtainable.

Autopsy (No. 900; performed July 25, 1928). *External Appearance*. Medium-sized female, elderly appearance, moderately muscular and adipose. Skin and conjunctiva were light lemon-yellow in color.

Brain. Basilar vessels showed tiny yellowish-white plaques on intima.

Abdomen. On opening the abdominal cavity, slight amount of gas escaped; no fluid was present. Peritoneum smooth and glistening. Firm, white, thin adhesions between the capsule of the spleen and abdominal surface of diaphragm. Firm white adhesions, separated with difficulty from the neighborhood of the distended gall bladder which was the size of a man's fist. Pelvis clear. White, firm adhesions around the tip of the appendix. Fine fibrinous adhesions between intestinal loops.

Chest. Pericardium free. Few scattered adhesions of both pleuræ, especially at apex.

Heart. Small and soft. Valves and chambers free. Fat infiltration of right ventricle.

Left Lung. Pleura smooth except in regions of adhesions. Surface: grayish blue with numerous blackish spotting. At the apex, about the size of an apple, the lung was firm in consistency, airless. On section, this area was slaty-black in appearance—no fluid expressible. Numerous pin-head gray nodules, dry and fragile, were found in this mass. Remainder of lung, dark red in color. Pulmonary vessels wide, walls thin. Lymph nodes at hilum were hard, pea sized.

Right Lung. At apex for a distance of about 2 inches in diameter the pleura was thickened.

Esophagus. At the height of the tracheal bifurcation, two bean-sized lozenge-shaped traction diverticula were found with few firm pea-sized bifurcation lymph nodes adherent to them.

Thyroid. Lateral lobes were 6 cm. long. Organ was firm, brownish red; on section, colloid containing.

Spleen. Measured 11 by 9 by 2.5 cm. Smooth grayish blue surface, soft. On section, soft, moist, violet-red pulp scraped away very readily. Markings not made out.

Appendix. Lumen of the apex for 3 cm. was replaced by whitish wall.

Suprarenals and Vessels. Free.

Kidneys. *Left:* 10 by 5.5 by 2 cm. Cortex and medulla distinct. Cortex, grayish-yellow, markings not distinct. Medulla, deep red, markings plainly visible. *Right:* 11.5 by 6 by 3.5 cm. Similar to left.

Uterus. Small, firm. Two small cervical polyps. Small amount of fresh blood in body.

Pancreas. Average size. On the surface and around it, numerous scattered small areas of fat necrosis were found. On section, similar areas were found throughout the pancreas.

Liver. Measured 25 by 16.5 by 15 cm. and was of average size. The capsule was thin. The lateral 5 inches of the anterior surface of the organ presented a mottled purplish-red appearance, being discolored by this ovoid area which narrowed toward the lower border. Numerous small conglomerate greenish-yellow tiny areas were scattered throughout. The remainder of the right lobe and the entire left lobe were brownish-yellow with a pinkish-red network in them (dilated capillaries). The posterior and inferior surfaces were similar.

On section, the left lobe of the liver and the left quarter of the right lobe were yellowish-brown in color. The markings were indistinct. The area that was purplish-red in color was well demarcated by an irregular wavy line that ran at an angle of about 20 degrees from the coronal section of the midportion of the liver, posteriorly and inferiorly. Roughly, one half was purplish-red in color. The remainder of the cut surface was a yellowish-brown. Irregular moth-eaten yellowish-green areas about 1.5 cm. in diameter and smaller areas were scattered through the purplish area. The walls of these small areas were soggy, smooth in places but for the most part rough and were light to dark green in color. Practically all the large veins were filled with thrombi. Some of these were laminated. The larger arteries were filled with adherent dark-brown clots. The large ducts were wide, the mucous membrane pinkish and slightly thickened.

Gall Bladder. About two and one-half times the normal size. The peritoneal surface was covered by a thin adherent fibrinous exudate. On section, it contained about 100 small silvery-faceted stones and thick dark-green fluid. The wall was slightly thickened. The mucosa presented a mottled black and dark-green appearance as if necrotic. A large anthracotic lymph node was present near the neck of the gall bladder.

Bile Ducts. Dilated, the walls were slightly thickened with a pinkish-red lining membrane and contained yellowish-brown bile.

Hepatic Artery. The entire main artery and branches were free except for the right and left branches as the vessel entered the liver where a laminated dark-brown adherent clot was found. This extended deep into the liver tissue. The clot could not be easily separated from the vessel wall.

Hepatic Veins. The right tributary of this vein was filled from its origin in the liver for about 3 cm. by a dark-brown nonadherent clot.

Portal Vein. Reddish-brown adherent thrombus originating at the bifurcation and extending into the branches in the liver.

Bacteriologic examination of the spleen revealed Gram-positive bacilli, staphylococci, *Bacillus coli*, *Bacillus proteus* and streptococci.

Anatomical diagnosis: Cholelithiasis; diphtheritic cholecystitis; thrombosis of the portal vein, hepatic artery and branches of hepatic veins; acute cholangitis with cholangiectasis; cholangiectatic abscesses of liver; hemorrhagic infarct of the liver (large); fat necrosis of the pancreas; infectious splenic tumor; parenchymatous degeneration of heart and kidneys; healed tuberculosis L.U.L.; traction diverticula of esophagus; icterus.

MICROSCOPIC EXAMINATION. *Heart.* Cells swollen and granular, moderate brown atrophy, moderate fatty changes in the musculature.

Liver. Moderate congestion, granular degeneration and fatty changes in the regions beyond the infarct. The infarcted region is limited by hemorrhagic and leukocytic areas. In places periportally, larger and smaller areas of necrosis with extensive leukocytic infiltration are found. The bile ducts show desquamation of mucous membrane and in some areas regeneration of the bile ducts is present. In places, the smaller vessels are filled with leukocytes and the endothelium is invaded by them.

Gall Bladder. Bluish thick layer of fibrin on an almost absent mucous membrane. Slight leukocyte reaction in this fibrotic region and in the wall of the gall bladder.

Portal Vein. Filled with a network of fibrin engulfing numerous degenerated leukocytes with red blood cells at the periphery. The adjacent tissue and wall of vessel are markedly infiltrated by red blood cells and leukocytes. The connective tissue and musculature contain pale pink-staining cytoplasm, with moderate pyknotic changes in the nuclei.

Hepatic Artery. Filled with fibrin, red blood cells, numerous degenerated leukocytes and a medium-sized area of canalization. The wall is infiltrated with leukocytes. The vasa vasorum are congested.

Pancreas. Larger and smaller well demarcated areas of fat necrosis are found.

Kidney. Capsule is thin. Tubules and glomeruli show marked replacement of the protoplasm by a granular pink-staining material. In places there are ghosts of glomeruli. The tubules are filled with a pale pink-staining material. Moderate fresh calcium deposits are present in the walls of some of the tubules. The smaller and larger vessel walls are moderately thickened and filled with pink-staining amorphous material.

Discussion. Lesions of the hepatic artery are often overlooked by pathologists who do not open the vessel for its entire length as a routine. This may partly account for the rarity of hepatic artery thrombosis in the literature.

These rather rare and unusual cases reopen the subject of lesions of the hepatic artery and the effects of its ligation in animals and in man. This has been a very fertile field for physiologists since Simon de Metz,¹⁰ in 1828, first ligated the hepatic artery in pigeons. Cohnheim and Litten¹¹ and Doyon and Dufourt¹² produced experimental thrombosis of the hepatic artery with subsequent necrosis of the liver by tying off the main artery and its branches. Segall,¹³ in an extensive dissertation on the liver circulation, reviews the literature and stresses the importance of proper surgical ligation. He reached the conclusion that the hepatic artery might be ligated in the human in its main stem proximal to the gastric artery without notable effects on the nutrition of the liver. Ligation distal to the gastric artery when the hepatic artery is previously healthy, results in more or less extensive necrosis and eventual total necrosis must be feared. Necrosis of the liver occurs when there are no accessory hepatic arteries, no unusually large collaterals, or from sudden total

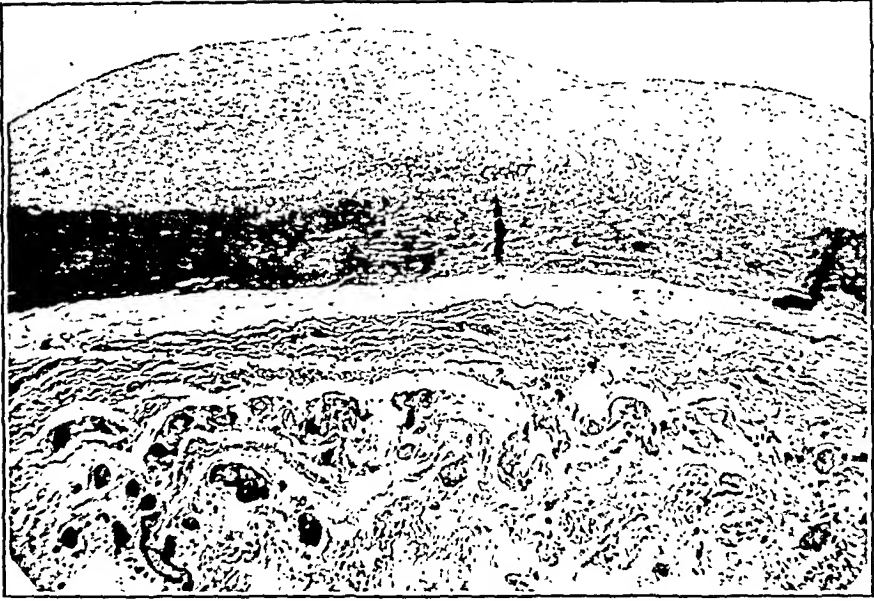


FIG. 1.—Aorta of Case I showing atheromatosis.

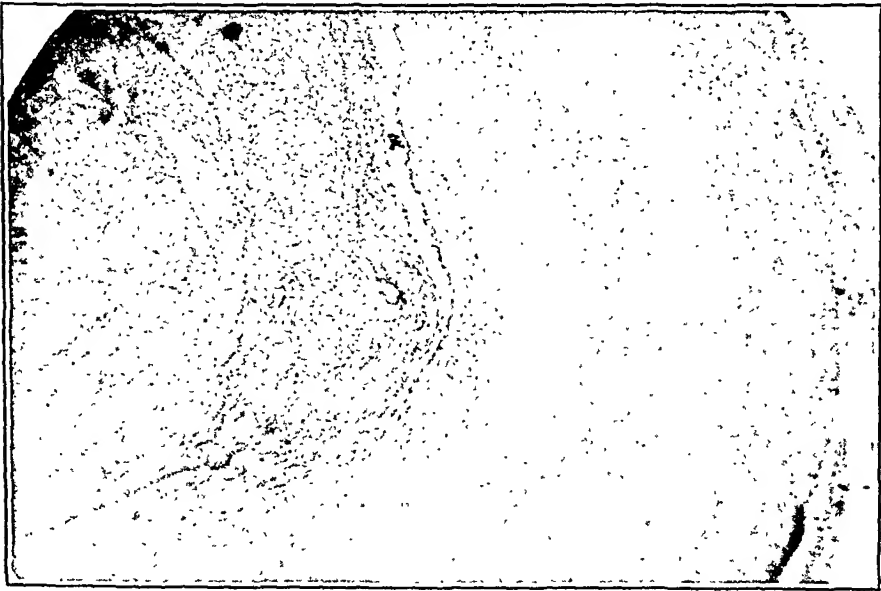


FIG. 2.—Hepatic artery of Case I showing atherosclerosis and occluding thrombus.

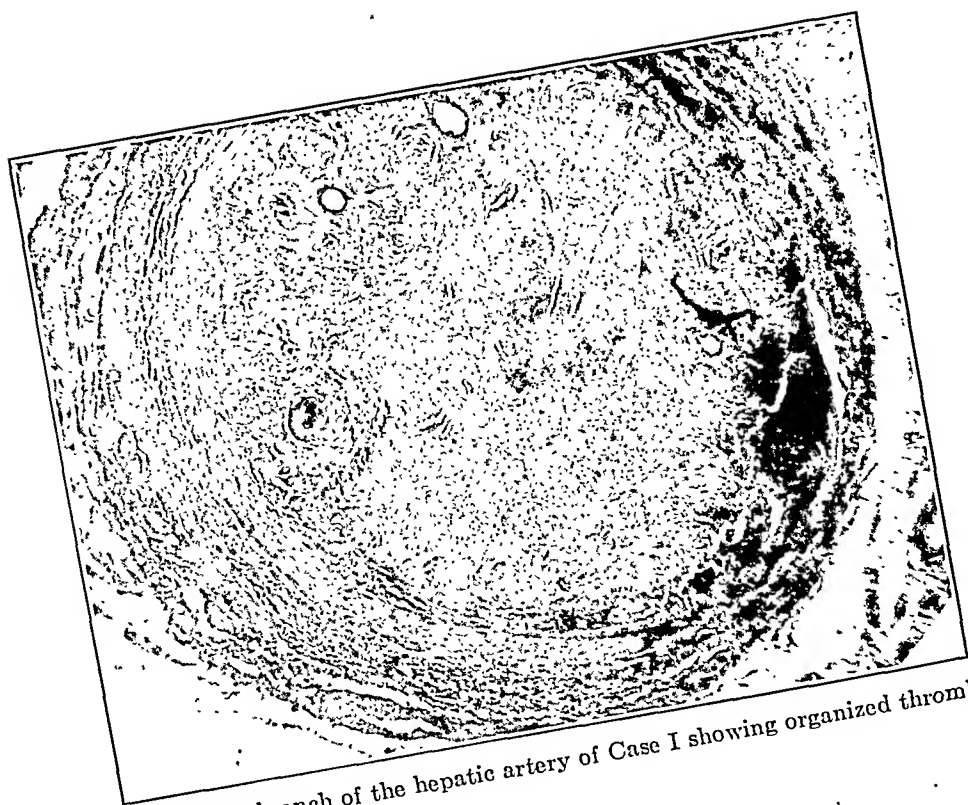


FIG. 3.—Right branch of the hepatic artery of Case I showing organized thrombus.

obliteration of the flow. Arterial blood is essential to the life of the liver substance.

Nicoletti¹⁴ offers the explanation that the broad junction of the hepatic lobes with each other in man makes it possible to ligate separately the final branches of the hepatic artery, but Narath and Thole¹⁵ believe the dangers of necrosis are too great to permit separate ligation of these branches.

Narath¹⁶ has reported 20 cases of ligation of the hepatic artery or its branches. Two cases (Socin and Salzer) died within seven hours and showed no necrosis of the liver at autopsy. Two cases had the portal vein as well as the hepatic artery ligated (Sprengel, Guibe and Herrenschmidt) with necrosis of the liver and death. Kehr, in 1903, ligated the hepatic artery for aneurysm of that vessel, the first time it has been reported with recovery. He ligated the main branch or its branches on three further occasions with similar results. Tuffier, ligating the hepatic artery for aneurysm in a man, aged seventy-two years, found necrosis of the liver at autopsy. Wendell ligated the vessel distal to the gastric branch with resulting total necrosis of the liver and death in thirty-six hours. In three cases the right or left branch (Bakes, Allesandri, Palacio) was ligated with recovery. Narath, Wilms and Tichow did the same operation and found necrosis of the lobe of liver at autopsy. Haberer and Wendell removed a lobe of the liver after tying off the corresponding arterial branch with favorable results. Klose carried out the same procedure and attributed the death to endocarditis.

Kaeding¹⁷ ligated the hepatic artery for aneurysm with a favorable result. Behrend¹⁸ tied the hepatic artery on both sides in a boy, aged six years, who had been run over. No autopsy was performed after the boy died with a clinical picture resembling acute yellow atrophy. Anderson¹⁹ ligated a branch of the vessel for aneurysm with uneventful recovery from this operation. Smith²⁰ tied off the artery for bleeding in an hepatic operation, the patient recovering. Hofmeister²¹ ligated the artery at the gastric branch for hemorrhage with a similar experience but Holst,²² in a gastric operation, lost the patient with necrosis of the left lobe.

These experiences do not lend themselves to very definite conclusions. However, ligation seems to be the best method of treatment for aneurysm of the hepatic artery. A well developed collateral circulation occurs in this or any other similar type of injury of long standing and might allow ligation at any portion of the vessel. When one branch is ligated, removal of the corresponding lobe, especially if lesions are found, is advisable. In extensive adhesions around the liver, the collateral circulation might be sufficient to allow ligation of the artery near the celiac axis. Bourdenko²³ has utilized this fact in animal experiments by suturing the omentum to the liver, thereby obtaining a collateral circulation and then after some days, tying the hepatica propria. The results are by no means conclusive, but he believes that the necroses are

less extensive. Villandre²⁴ attempted to avoid the danger by slowly constricting the artery before ligation.

Narath and Steckelmacher²⁵ studied histologic changes in the liver after ligation of the hepatic artery. Among the most important findings are periacinar connective-tissue proliferation and cyst formation, both described by Janson²⁶ also. It must be emphasized that this formation of connective tissue has nothing in common with true cirrhosis of the liver (Rost²⁷). Rabinovitsch²⁸ recently showed that the *arteria hepatica propria* anastomoses regularly in the transverse fissure with the accessory artery branching off from the *arteria gastrica sinistra* or the *arteria mesenterica superior*, adding another link in the anastomatic chain.

Summary. Two cases of thrombosis of the hepatic artery are reported. In one, an acute case, probably secondary to biliary-tract infection, there was involvement of the portal and hepatic veins, a hemorrhagic infarct in the liver and the hepatic artery showed a thrombus at its bifurcation extending into the liver. In the other, a more chronic case, probably of atherosclerotic origin in a man with thromboangiitis obliterans, the main artery was involved, no infarct was present. The patient probably did not die from this condition.

The clinical and experimental evidence would suggest that the degree of liver injury following occlusion of the hepatic artery depends in part upon the site of the occlusion and in part upon the extent of the collateral circulation.

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THE MEDICAL OR INJECTION TREATMENT OF VARICOSE VEINS.*

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THE idea of obliterating varicose veins by the injection of drugs occurred to Provatz in 1851.¹ Such blood coagulating solutions as perchlorid of iron, alcohol, tincture of iodin and Pregl's (isotonic iodin) solution were first tried, with resultant reactions, infections and fatalities. De Lore,² in 1894, showed that success was due to the reaction of the drug on the intima and not the coagulation of the blood. In 1911 P. Linser³ introduced 1 per cent mercury bichlorid, and with his brother, K. Linser,⁴ changed to 20 per cent sodium chlorid solution in 1923, which they found safer because less toxic. About this time Sicard,⁵ in Paris, used sodium salicylate, while Kausch and Nobl,⁶ in Vienna, preferred invert sugar solutions.

After fifteen years' experience in the treatment of 48,000 cases it is now the accepted form of treatment in most of the European clinics. In this country results reported by Hayes,⁷ McPheeters,⁸ Bratrud,⁹ de Takats,¹⁰ Schussler,¹¹ Kilbourne¹² and the author¹³ prophesy its increasing popularity. They prefer the injection method to surgery because there is less cost to the patient, less pain, better cosmetic results, recurrences are less frequent, danger of embolism is less and the patient is ambulatory.

In a survey of 4607 operative cases, Kilbourne¹² finds 1 death in each 250. In 53,000 cases treated by the injection method, McPheeters¹⁴ found 11 fatal cases, to which Kilbourne¹² adds 2 more. This is about 1 in 4000 cases. Recurrences after operation average about 30 per cent compared with 7 per cent by the injection method. Some men take a half-way position, using surgical excision of certain varices with injection of the remainder. I can see no good reason for adding the dangers of surgery when the injection method alone can be used successfully in all kinds of varices.

Action of Sclerosing Drugs. The delayed acceptance of this method of treatment by the medical profession has been due to fear of emboli. Animal experiments by Doerfell,¹⁵ Regard¹⁶ and Bazelis,¹⁷ and removal of sclerosed veins in humans by de Takats¹⁰ and V. Meisen,¹⁸ have shown that an adherent, fibrotic clot is formed in the veins injected with sclerosing solutions. The irritating action of the latter causes a destruction of the intima followed by a trabecular deposit of fibrin and blood platelets resulting in an adherent, dense, fibrous clot, often extending into offshooting branches, in which organization with connective-tissue formation proceeds and

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progressive retraction takes place, finally resulting in a thin, fibrous strand in which only a few muscle fibers are demonstrable. This explains the paucity of emboli. The mechanism of the action of obliterating injections and the pathologic changes in the veins have previously been described by Forestier¹⁹ and the author.¹³

Nature of Sclerosing Drugs. Various drugs are being used by various men to accomplish the same result, namely, a hard, firm, permanent fibrosis of the vein. I will briefly summarize the characteristics of the most popular ones.

Bichlorid of mercury, the first drug used to obliterate veins, is little used now because of its toxicity and severe sloughing if some is accidentally injected into the tissues. Only one injection can be given at a time and the small amount injected results in only a small sclerosis, thus requiring many injections; 1 cc. of a 1 per cent solution is the maximum amount that can be given at one time. The same objections apply to red mercury iodid and mercury cyanid.

Sodium chlorid is still used routinely in some clinics here and abroad, but most men have given it up in their private practices because of the severe painful cramps immediately following injection, severe sloughing if injected outside a vein and frequency of "perivenitis." I use it occasionally in "intima resistant" cases (which I described in a former paper), giving 5 to 10 cc. of a 20 to 35 per cent aqueous solution. Linser and others find that multiple injections requiring larger amounts increases the danger of embolism.

Sodium salicylate, introduced by Sicard,⁵ is used quite extensively in France by Forestier¹⁹ and others. The usual amount given is 5 to 10 cc. of the 20 per cent or 2 to 6 cc. of the 25 to 40 per cent aqueous solution. I have found that a moderate degree of a burning pain lasting thirty to sixty seconds occurs immediately after such an injection. If less than 5 cc. of the 20 per cent is injected very little pain is experienced, according to Bratrud.⁹ Of course, a slough is produced if any amount is injected outside the vein, especially in strengths greater than 20 per cent. If larger amounts or a stronger solution is used the pain is greatly increased and complained of by most patients. I prefer sodium salicylate in strengths of 20 to 35 per cent in cases where the intima resists the irritating action of repeated injections of invert sugar preparations, given with careful technique. Sclerosis is obtained in a high percentage of cases after the first injection with the 25 to 35 per cent strengths.

Sugar solutions have been used since 1923 in the forms of *glucose* and *invert sugar*. They cause little or no pain (slight muscle cramps or tight feeling in leg in 30 per cent in author's series) are nontoxic and result only in a painful, indurated area *without sloughing* if injected *outside* of a vein, which is relieved in a few days by frequent applications of wet heat. Painful perivenitis is less frequent than

TABLE I.—ANALYSIS OF VARIOUS FORMS OF TREATMENT.

Drugs used.	Mercuric chlorid.	Sodium chlorid.	Sodium salicylate.	Invert sugar.	Invert sugar and sod. salicyl.	Calorose.	Glucose.	Quinin-urethane.
Concentration used, per cent .	1 0.5	20 25 30-40	20 20 25 35 50 60 70		50-60-70 5-10-15	40-60	50	
Usual dose, cc.	1 2	10 5 5	2- 5- 3- 2- 5 10 6 5	10- 10- 20 20 10	5-10 5-10	10-20	10-20	1-2
Toxicity	VS	s m m	s s s s	o o o o	s s	o	o	m
Cramps or pain	o	S VS VS	s m S VS	o s s	o s	s	s	m
Action on intima	m	m S VS	m m S VS	m S S	S VS	m	m	m-S
Efficiency, per cent	70 60	70 90 97	78 90 97	78 85 90	80 93	60-70	60	70
Slough	S	S S S	m m S S	o o s	s s	o	o	S
Periphebitis, per cent5	15 20 25	5 5 10 12	3 5 8	3 5	5-8	5	
Indications	Diabetes in- tima; resis- tant cases	Diabetes in- tima; resis- tant cases; routine ?	Diabetes intima; resistant cases; routine	Routine	Routine	Routine	Routine	Small veins; selected cases.
Contraindications	Nephritis; P.O. cases; pregnancy; art.scler.; feathery veins	Neurotics; P.O. cases; feathery veins	Idiosyncrasy	Untreated diabetes	Untreated diabetes; idiosyncra- sy	Untreated diabetes	Untreated diabetes	Pregn.; idio- syncrasy.

o, none; s, slight; m, moderate; S, strong or severe; VS, very strong or severe.

with the more caustic solutions. I have noted that formation of the thrombus may proceed more slowly with sugar solutions, but, finally, firm organization results. Glucose, because of its high viscosity in strengths over 50 per cent requires such a large needle that it is impractical except for larger veins. In my hands, a comparatively low percentage of sclerosis obtained after the first injection. De Takats¹⁰ and others prefer it as a routine. Invert sugar is the natural chemical combination of equal parts of dextrose and levulose with 3 to 5 per cent sucrose resulting from the hydrolysis of cane sugar. Nobl⁶ has led the way in popularizing its use. He has reported great success in over 10,000 injections without a fatality. It is dispensed in Europe under the name of calorose, and in this country as invertose or invert sugar, in 10-cc sterile ampules ready for injection; the calorose in strengths of 40 and 50 per cent, the invert sugar and invertose in 50, 60 and 70 per cent. Its decreased viscosity compared with glucose is its chief advantage over the latter, allowing it to be easily injected in strengths of 60 to 70 per cent through a 20-gauge needle, thus resulting in a higher percentage of successful sclerosis after single injections in small as well as large varices. I used 50 to 60 per cent invertose routinely in my first 450 cases, with successful sclerosis after initial injections in 85 per cent, careful technique being observed. In the remaining 15 per cent repeated injections of 60 to 70 per cent invertose, sodium chlorid or sodium salicylate, 25 to 35 per cent, gave sclerosis. The fact that sugar preparations are "just sugar," nontoxic and almost painless, make them popular with the patients.

During the past three months I have been using a new preparation (invertose compound). It is a combination of 50 to 60 per cent invert sugar with 5 to 12.5 per cent sodium salicylate. I have now used it in about 100 cases—600 to 700 injections—and am quite enthusiastic about it. The sodium salicylate increases the irritant action on the intima, resulting in a firmer and higher percentage of sclerosis, without increase in pain or danger of necrosis if small amounts are injected outside the vein. The sodium salicylate also decreases the viscosity, allowing stronger solutions (60 to 70 per cent) to be injected through smaller needles.

Quinin-urethane solution, in doses of 2 cc., was advocated by Genevri²⁰ and Douthwaite.²¹ Immediately upon injecting into the vein, a severe prickly burning sensation is felt for an instant at the point of injection. Because of its short duration, the pain is usually not objected to. It is toxic, especially to patients sensitive to quinin and pregnant women. Kilbourne¹² reports 5 cc. killing a 7½-pound rabbit. Sclerosis is not certain. I find it limited almost to small "pick-up" veins remaining after a general closure.

Metaphen has been recommended by Schussler¹¹ for small veins. I have had no experience with it.

Varicophytin is a European product of sodium chlorid combined with an opiate to relieve the pain caused by the former. I have been unable to obtain any of it myself or to find any reports of its use in the literature.

Forestier¹⁹ has rightfully stated that each varix has its own reactive power which is independent of the degree of dilatation. The physician must decide in each case the concentration of the sclerosing agent and use the weakest solution that will prove efficient.

Technique of Injection. This varies somewhat according to the location, size, nature of varices, equipment of physician and solution used. I mention first some general rules which I have found from experience to be helpful. Large varices, especially if long, should first be injected near their lowest point and so closed upward, but never injected higher than the middle of the thigh. Clumps, plexes or masses of large varices usually found over the calf of the leg are prone to develop perivenitis, so strong caustic solutions should be avoided, especially in large amounts. Sugar solutions are safest. I use an iron ring, 2 or 3 inches in diameter, pressed firmly against the leg to keep the solutions from escaping.

It is hard to prophesy how a vein will sclerose, as some large veins close extensively from a weak injection, while some small veins may need repeated injections of increasing concentration at the same point. It is safest to start with weak solutions.

In case of ulcers, always inject their feeders first, inserting needle at point well away from the inflamed infected area. Feeders may enter ulcer area from any angle, and frequently run under the ulcer.

In case of very large varices, I add 2 or 3 minims of sterile 1 to 1000 adrenalin solution to 20 cc. of the stronger invert sugar preparations (60 to 70 per cent) to cause contraction of the vein, and then apply elastic bandage to keep them collapsed. This hastens cosmetic results.

It is safest not to give more than two injections at a sitting, that is, one in each leg. I consider 40 cc. (two 20-cc. doses) of any of the invert sugar solutions (60 to 70 per cent), or 20 cc. of the invert sugar and sodium salicylate solution, an advisable *maximal* dose. The literature shows that many of the cases of reported emboli followed where many injections were given at one sitting.

Nonsclerosis is due to poor technique or increased resistance of the intima to the irritating effects of the sclerosing agent, an individual characteristic.

Expect a slough in all cases where extravenal accidental injection has occurred, except when sugar solutions are used, and dilute solution in the tissues liberally by injecting normal saline and massage area five to ten minutes.

Test patency of deep veins by Trendelenburg and Pratt methods before injecting in suspicious cases. Never inject where deep veins are closed.

Advisability of treatment and prognosis should be guarded in cases of hard chronic edema or elephantiasis.

Good results have been obtained by various men using somewhat different technique. The main thing is to get the solution in contact with the intima of the varix with the least dilution by the blood. While the patient stands erect so as to distend his veins, the point of injection is selected and marked with 1 per cent mercurochrome. A rubber tourniquet is now applied well above this point. The patient then lies prone on a table with an adjustable leg-rest. The skin is sterilized as for any intravenous injection. A sharp sterile needle, 18- to 24-gauge, according to size of varix, attached to a sterile glass Luer syringe, filled with the solution at body temperature, is carefully inserted into the marked varix. Blood is aspirated to be sure the needle is well within the vein. The tourniquet is now removed, relieving the distention. The assistant with index fingers now carefully "milks" the remaining blood from a section of the varix for a distance of a few centimeters above and below the needle, being careful not to disturb the latter. After assuring oneself that the needle is still in the vein, inject the solution rapidly enough to produce slight distention. The amount required will vary from 5 to 20 cc. (in case of invert sugar preparations), depending on size of varix. Keep fingers of assistant and needle in place for five minutes. Apply sterile pressure gauze pad with adhesive strips where needle was removed. If veins are large and prominent apply a larger nonsterile pressure pad over section of vein expected to become sclerosed and hold in place by rubber elastic bandage from ankle to thigh, kept on for one to two weeks, and only removed during the time of subsequent injections which can be given bi- or tri-weekly. This allows veins to become sclerosed in a collapsed condition, giving quicker cosmetic result. Instruct the patient to get up and go about duties as usual to attain best results.

Usually twenty-four to forty-eight hours after an injection one of the following results will occur: (1) No sclerosis; (2) only thickening of vein wall without obliteration of the lumen; (3) complete sclerosis and obliteration of vein lumen resulting in a tender fibrous cord; (4) same as (3), with "perivenitis" (described later). In the case of (1) and (2) repeated injections at some point with increasing concentration of solutions must be made.

Observations and Results in Five Hundred Cases. The following is a brief summary of my observations and results in 500 cases with over 5000 injections, occurring in private practice since February, 1927. This is a considerable increase in the number of injections per patient over our preliminary report. The ages varied from seventeen to seventy-nine years, most of whom were females. A careful history was taken on all the cases, especially with regard to local symptoms, previous internal or external phlebitis and con-



FIG. 1a.—Mr. H. A. Before treatment.



FIG. 2a.—Mr. W. W. Before treatment.

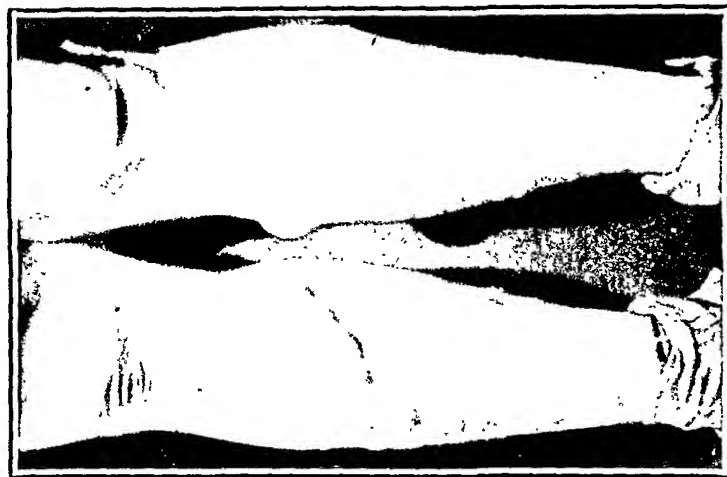


FIG. 3a.—Mr. S. S. Before treatment.

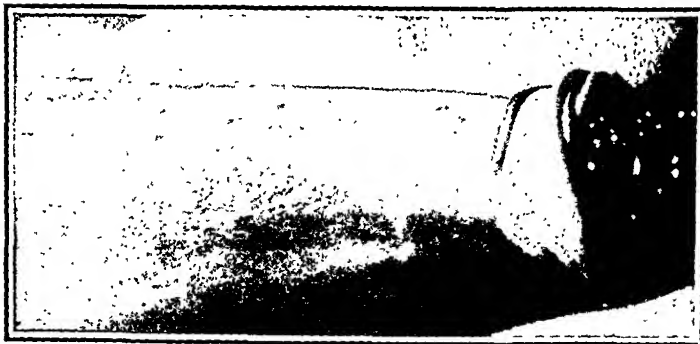


Fig. 1b.—Mr. H. A. After treatment. (Two months).

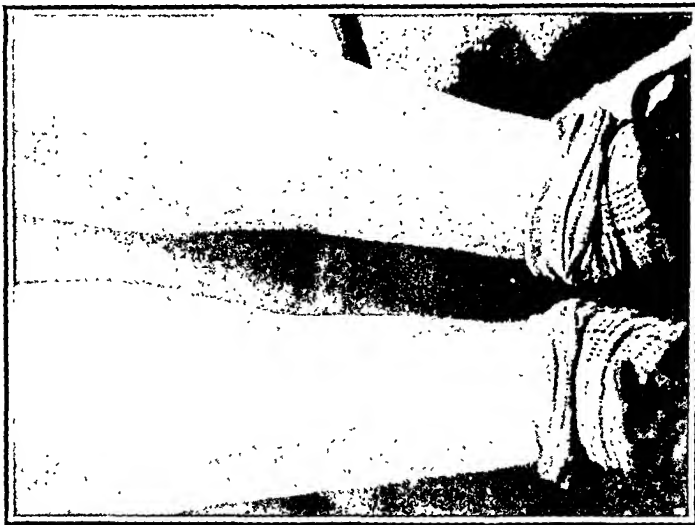


Fig. 2b.—Mr. W. W. After treatment. (Four months).

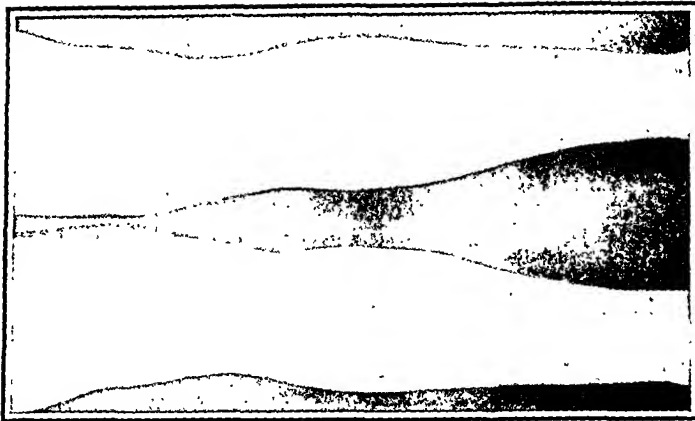


Fig. 3b.—Mr. S. S. After treatment. (Six months).

stitutional diseases. A urinalysis was done on all cases, and a physical examination when indicated. Whenever a previous internal phlebitis was ascertained or suspected, a Trendelenburg test and that advocated by J. P. Pratt for patency of the deep veins was done. The latter test consists of closing off the circulation in the superficial veins by firmly applying an elastic or Ace bandage from ankle to thigh; then have the patient walk for about a mile. If the deep veins are blocked then all venous circulation is cut off and severe pain will result. If the patient returns in comfort the deep veins must be open. I prefer this test and believe it to be reliable.

The chief complaints were edema, dull aching pains or severe periodical cramps, heaviness of legs, cold feet, ulcers, phlebitis, subcutaneous hemorrhages, rheumatic-like pains about knees or ankles, eczema and periostitis. When *disturbed arterial circulation* or *other diseases*, such as cardiac decompensation, *were not* an added factor, these symptoms disappeared on closure of the varices. Elderly patients, especially, spoke of their legs feeling "twenty years lighter." (Figs. 2a, 2b.)

Thirty per cent of the patients gave a history of varicosities in one or both of the parents or grandparents, pointing toward a hereditary etiological factor. Time will not allow further discussion of the question of etiology.

Twenty-six per cent of the patients had the veins treated for cosmetic reasons. Results in these cases were most gratifying. (Figs. 3a, 3b.)

Thirty-five cases showed ulcers. Infective and luetic causes being ruled out, these ulcers showed varices as their only cause. The most common locations were about the malleoli, as this is the source of saphena magna and parva, and the base of the stagnant venous column. Varicose ulcers always have a varicose vein extending into base from above, lateral or even below, which "feeds" it, and whose closure results in permanent healing. (Figs. 1a, 1b.) Skin grafts may be used in very large ulcers after wet packs of 1 to 4000 mercury cyanid solution have cleaned up any infection. Application of pressure to the ulcer by an ordinary rubber bath sponge and rubber elastic bandage, as suggested by Nobl,²² is a great aid and gives almost miraculous rapidity of healing. Unna's paste boot is often a great asset, especially if a chronic obstructive lymphangitis exists, and can be used to advantage for support several weeks after ulcers are healed. In cases of marked edema it is best to examine after a preliminary bed-rest period to reduce the swelling, when the true location and extent of the varices can be determined.

Five cases showing phlebitis of the superficial veins were treated in the usual manner. No injections were deemed advisable for *at least six months* after the acute inflammation had subsided.

Eczema must be treated as usual in addition to closing the varices.

Ten cases of apparent chronic obstructive lymphangitis were encountered. They were carefully studied, injecting only varices definitely responsible for some of the edema, and advising the usual supportive measures (Unna's paste boot—elastic stockings or bandages). Prognosis was very guarded.

Serious complicating conditions, such as diabetes, nephritis, hypertension with decompensating heart and so forth, should be treated first and injections given later, if at all, depending on improvement in general condition.

Painful varices below lower one-third of thigh may be treated in pregnant women in the early months with comparative safety, sugar solutions preferred.

One case of varices in legs was cured by removing a large ovarian cyst.

Eight cases were refused injection treatment because of complications already mentioned.

Eleven cases previously operated upon were injected successfully. I warn against the use of the more caustic solutions in these cases as the recurrent veins often have abnormal intimæ.

No embolisms were observed. Three severe sloughs occurred (2 with chlorid of sodium, 20 per cent, and 1 with 1 per cent chlorid of mercury) due to extravascular accidental injection. Surgical excision of slough was done in 1 case with good result.

Twenty-five times moderate to severe periphlebitis followed injections. This is a painful, red swelling along the course of the sclerosed vein, and may involve the entire saphena magna or parva. I believe it to be due to using too caustic solutions on a supersensitive intima, so I now always first try 5 to 10 cc. of a 50 per cent invert sugar preparation to pick up these types. The best treatment is rest and hot wet packs. All veins of any size are naturally somewhat tender for a few days after closure. If closure is extensive this soreness is increased in area and time of course.

Recanalization and return of some of the varices occurred in about 5 per cent after one or two years. These were easily closed again, but more caustic solutions were usually necessary. Improvements in technique and more thoroughly extensive original treatment may reduce this figure.

Based on a plain question to the patients, 98 per cent stated they were satisfied with their results.

Summary. 1. The injection method of treating varicose veins, although comparatively new in this country, is well established and has been widely used in Europe for the past ten years.

2. It is safer, cheaper, less painful and more permanent than surgery.

3. Of the various sclerosing agents, sugar solutions, especially

preparations of invert sugar, are safest for routine use, and best for beginners.

4. A careful technique must be worked out in order to bring the sclerosing solution in contact with the intima with the least possible dilution for five minutes.

5. "Intima resistant" cases occasionally occur, and here the more caustic solutions can be used to advantage.

6. A survey of experience and results in 500 cases with over five thousand injections points to the desirability and an increasing acceptance of this method.

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BLOOD REGENERATION IN SEVERE ANEMIA.*

XXI. A LIVER FRACTION POTENT IN ANEMIA DUE TO HEMORRHAGE.

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AND

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THIS paper deals with a liver fraction which weighs but 3 per cent of the original whole liver yet contains 65 to 75 per cent of the potency of whole liver, as measured by new hemoglobin production in long-continued anemia in standardized dogs. The data here presented deal only with the simplest form of experimental anemia due to bleeding, but it is at least probable that this liver fraction is potent in certain types of human anemia. Observations made in various medical clinics must decide what usefulness it may have in human anemia. The secondary anemia fraction as prepared for this work is palatable and can be ingested in large amounts without any clinical disturbance.

In 1920, Whipple, Robbins and Hooper¹¹ reported that liver feeding had a very favorable influence on the production of hemoglobin and red cells in dogs during short anemia periods. Since that time Robbins and Whipple have shown that liver feeding has an extraordinary effect on hemoglobin and red-cell production in severe long-continued anemia due to hemorrhage in dogs. During this considerable period Whipple and Robbins have tested a great variety of liver fractions and extractives. Some of these experiments were reported three years ago.⁹ More recently with the coöperation of Dr. Sperry and Mr. Elden of the Department of Biochemistry, we have reported⁴ a considerable series of liver fractions and extracts which contained much of the potency of the whole liver as measured by new hemoglobin production in severe experimental anemia.

That more than one factor is concerned in this favorable reaction to liver and other food factors is obvious from some earlier experiments¹ in this laboratory which show that the inorganic ash of liver, kidney and apricots is potent in this type of secondary anemia. It was shown that the liver and kidney ash contained about half the potency of whole organs. Probably the contained iron is responsible

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for a considerable portion of this favorable reaction noted with organ ash.

Recently a liver fraction known to be fully potent in human pernicious anemia (Liver Extract No. 343 N.N.R. prepared by Eli Lilly and Company) has been tested in this type of secondary anemia. It was found by Robbins and Whipple³ that this pernicious anemia liver fraction contained not over 10 to 20 per cent of the potency of whole liver for the production of new hemoglobin in severe secondary anemia.

Ever since it was firmly established that liver and kidney were rich in materials which contributed so effectively to the production of new hemoglobin and red cells, we have had a logical interest in all fractions obtained from liver or kidney. With ordinary laboratory facilities the production of liver fractions in sufficient amounts to permit of their standardization in dogs is a very difficult task. It was obvious that commercial laboratories could do certain work with great advantage over the school laboratory. Dr. Clowes and Mr. Walden became interested in our problems and offered the facilities of Eli Lilly and Company's Research Laboratories. These laboratories were engaged in the commercial preparation of a liver fraction (No. 343 N.N.R.) potent in pernicious anemia. The results of our work with liver fractions⁴ were carefully studied and with this knowledge it was decided to test some liver fractions which were already at hand in the Eli Lilly Laboratories in sufficient amounts for work with anemic dogs.

It is obvious that further purification with study of the various substances contained in the secondary anemia liver fraction will give interesting information. We hope to report on this subject from time to time.

Methods. The general methods used in these experiments have been described in sufficient detail in the first,⁷ fifth⁸ and sixteenth¹⁰ papers of this series. The standard bread used in all control periods and elsewhere as indicated is described as to ingredients and preparation. This bread contains wheat flour, starch, bran, sugar, cod-liver oil, canned tomatoes, canned salmon, yeast and a salt mixture. Bread (S) which contains a little salmon was used in all the experiments here recorded. This bread is a complete diet for an adult dog and will maintain a dog in health for long periods of time, if not indefinitely. This ration keeps the hemoglobin production at a very low level, the average being close to 1 to 3 gm. of hemoglobin per week period over and above the unknown maintenance factor. There are individual differences and some dogs are constantly high in hemoglobin production on the basal rations as well as other diets. The *hemoglobin index* in these papers is a figure obtained by dividing the hemoglobin per cent by the red-cell hematocrit in per cent. We believe this figure gives information of value as to the saturation of the red-cell stroma with hemoglobin.

It is important to remember that these standard dogs are in a condition of sustained anemia (40 to 50 per cent hemoglobin) month after month, year after year. Some of the dogs have been *continuously anemic*, as indicated for four to five years, and are reacting quantitatively to various specific diet intakes in the fourth year as they did in the first year. The experiments given in the tables are taken out of the dogs' experimental history, which is continuous. The figures given represent the observations made at the *end of any given week*, so that hemoglobin figures noted for the first week of any feeding represent the production of hemoglobin due to seven days' feeding of that diet as indicated.

The *reserve storage of hemoglobin factors* is another important point which bears on the interpretation of results. It is surprising to observe how difficult it may be to exhaust this emergency reserve in the healthy dog. We have made it a rule to produce our experimental anemia slowly over a two- or three-week period and to maintain this anemia for two or three months on the standard bread diet to insure the exhaustion of this reserve. During this period as much as 250 to 350 gm. of hemoglobin may be removed by bleeding, representing a tremendous reserve which can scarcely be stored as finished red blood cells. This reserve is probably stored as intermediates which on demand can be combined to form the finished blood hemoglobin. After this period the dog will react with a small and constant hemoglobin output to the standard bread diet and will react uniformly to various diet factors as given in preceding papers.

Hemoglobin production, due to any given diet period, is calculated as follows: The hemoglobin level at the end of the fore period or last bread-control week is compared with the hemoglobin level at the end of the after period. If these hemoglobin levels coincide within 2 or 3 per cent no correction is needed, but if the figures are 3 or more per cent apart we correct for this difference in hemoglobin level. As calculated above, a 10-kilo dog has in circulation about 55 gm. hemoglobin at a hemoglobin level of 50 per cent: Therefore we allow a gram of hemoglobin for each per cent difference of level. For example a dog shows a 50 per cent hemoglobin level at the end of the fore period but in the after period is bled slightly too much, which reduces his level to 43 per cent. Obviously we cannot attribute this 7 gm. of hemoglobin to the given diet but to the overbleeding. We deduct this 7 gm. from the tabulated figures to give a correct figure for hemoglobin production on the given diet. Experience shows that this calculation gives an accurate approximation of the actual findings when known amounts of hemoglobin are abstracted from these anemic dogs.

The total hemoglobin production due to any given diet is readily calculated from the tables. The control bread periods show $1.5 \pm$ gm. hemoglobin production each week. This amount of

hemoglobin is removed for the routine determination of blood volume and hematocrit and some dogs will produce a little more than this amount of hemoglobin per week as the control level. The average value must be very close to 2 gm. per week in our large colony. We deduct this 2 gm. from each week's output above this figure and this includes the two weeks' feeding period plus the two or three weeks after control period. It has been amply proven² that on a favorable diet a dog stores substances which later, during the unfavorable control diet or after period, will be turned into hemoglobin and appear often in considerable amounts above the control level. This hemoglobin production of the after period obviously is due to the favorable diet or drug and is added to the hemoglobin production of the actual diet period. There is always more or less lag between the start of a favorable diet period and the rise in the curve of the hemoglobin production. That there is a lag in the fall of the hemoglobin production after any favorable diet period is not surprising. We may choose to explain this lag as due to the complicated internal metabolism of hemoglobin which must be built up from a variety of building stones present in the intestinal contents or stored in the body.

The secondary anemia fraction was prepared as follows: Fresh hog livers were finely ground into water containing dilute sulphuric acid. The mixture was then heated to 80° to 85° C. and filtered. The filtrate was evaporated in vacuo to a thick syrup and precipitated with 70 per cent alcohol. The portion insoluble in 70 per cent alcohol was dried and designated the secondary anemia fraction. This represents 3 per cent the weight of the whole liver or about 10 per cent of the dried liver weight.

The ashing was carried out in a muffle type of furnace using gas as fuel. A quantity of the secondary anemia liver fraction was placed in evaporating dishes and the temperature gradually raised over a period of about two hours to 1200° to 1300° F., held at this temperature for three hours and allowed to cool, requiring about twelve to fifteen hours. Under the above condition an easily powdered light-colored ash was obtained with practically no loss due to fusion.

Experimental Observations. When one works with fractions obtained from a fresh organ and attempts to extract a potent factor from a mixture rich in protein it is usually found that the residue contains a sizeable portion of the substance under investigation.⁴ Moreover when a variety of fractions are made from a single lot of organ "Brei," it is not infrequent for the activity of the individual fractions to exceed the total activity of the original "Brei." This may be due to inaccuracy of the methods of testing the active principle or it may be due to some changes effected in the original mixture by the chemical processes—in other words the method of preparation may unlock substances which are held in the protein

matrix of the original organ mixture. These points are illustrated in Tables 211 and 212.

TABLE 211.—POTENCY OF LIVER FRACTIONS IN EXPERIMENTAL ANEMIA.

OUTPUT OF HEMOGLOBIN GIVEN IN GRAMS PER TWO WEEKS' FEEDING.

Dog No.	Secondary anemia fraction.		Pernicious anemia fraction.		Residue.	
	Hemoglobin produced 2 weeks, gm.	Liver equivalent daily, gm.	Hemoglobin produced 2 weeks, gm.	Liver equivalent daily, gm.	Hemoglobin produced 2 weeks, gm.	Liver equivalent daily, gm.
23-1	62	300				
24-2	88	300				
27-241	77	300	39	300
27-235	94	300				
24-59	94	300	42	300
25-23	43	300				
24-25	47	300	19	300		
27-241	69	300	24	300	68	400
24-45	78	300				
24-26	34	400	15	400		
24-26	47	400				
24-45	107	600				
24-59	99	600				
24-59	95	1000				
25-23	84	1000				
24-45	112	3000				
24-25	62	3000				

Table 211 gives a summary of the completed experiments dealing with liver fractions and residues. A certain number of experiments with the pernicious anemia liver fraction (Liver Extract No. 343 N.N.R. prepared by Eli Lilly and Company) are included for the sake of completeness. As reported elsewhere³ this pernicious anemia fraction usually contains about 10 to 20 per cent of the active secondary anemia principle. The residue has not been tested in many experiments but sufficient data are given to show that it contains a liberal amount of the active secondary anemia fraction. Apparently no methods of extraction are available which do not leave behind a good deal of this or other active principle—for example the substance potent in pernicious anemia.

Our main interest centers in the secondary anemia fraction column (Table 211) where a considerable variety of experiments are summarized. For the sake of a *base line* we may say that from the average of a very large number of experiments we expect to find 90 to 100 gm. *new hemoglobin* produced by a standard anemic dog as the result of a two-weeks period in which 300 gm. of pig liver are fed daily. Different dogs have individual peculiarities and are geared for greater speed in hemoglobin production and others fall

below the average hemoglobin production. These individual peculiarities are usually quite constant, just as a dog's capacity for running or work may be very different from a litter mate. Dog 24-45 may be cited as a dog whose production is abnormally active on any diet. Dog 24-26 shows an abnormally low output but this is due in part during the past year to a severe pyorrhea.

TABLE 212. — WHOLE LIVER, LIVER FRACTIONS AND RESIDUE IN 300 GRAM EQUIVALENTS DAILY.

Dog 27-241, COACH, FEMALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, bled, gm.
Bread, 350; salmon, 100; klim, 25 . . .	100	12.7	755	3.9	0.59	2.16	21.2	46	1.4
Liver fraction, secondary anemia* . . .	100	12.6	700	4.7	0.65	2.24	23.9	53	30.0
Liver fraction, secondary anemia* . . .	100	12.6	728	6.5	0.51	1.96	23.9	47	31.7
Bread, 350; salmon, 100; klim, 25 . . .	100	12.5	754	6.2	0.51	2.01	19.6	39	23.5
Bread, 350; salmon, 100; klim, 25 . . .	100	12.5	782	4.0	0.50	2.19	18.1	40	1.1
Bread, 350; salmon, 100; klim, 25 . . .	100	12.4	748	4.5	0.50	2.13	21.1	45	1.2
Whole pig liver**	100	12.2	708	7.4	0.68	2.19	28.3	62	50.2
Whole pig liver**	100	11.9	710	6.0	0.52	2.29	20.9	48	28.0
Bread, 350; salmon, 100; klim, 25 . . .	100	12.2	726	4.9	0.52	2.13	19.7	42	12.9
Bread, 350; salmon, 100; klim, 25 . . .	100	12.2	762	4.1	0.57	2.22	21.1	47	1.5
Liver fraction, secondary anemia† . . .	100	12.5	722	5.4	0.62	2.21	25.7	57	33.8
Liver fraction, secondary anemia† . . .	100	12.2	763	5.1	0.55	2.27	24.3	55	16.5
Bread, 400; salmon, 75; klim, 25 . . .	100	12.3	758	5.7	0.55	2.31	20.9	48	27.4
Bread, 400; salmon, 75; klim, 25 . . .	100	12.7	794	4.3	0.52	2.27	19.7	45	1.5
Liver fraction, pernicious anemia‡ . . .	100	12.7	766	5.7	0.48	2.08	21.8	45	15.7
Liver fraction, pernicious anemia‡ . . .	96	12.8	813	4.8	0.45	2.07	20.7	43	1.4
Bread, 400; salmon, 75; klim, 25 . . .	99	12.8	772	5.4	0.42	2.11	21.5	45	1.4
Bread, 400; salmon, 75; klim, 25 . . .	88	13.0	826	6.0	0.43	1.84	24.1	44	15.4
Bread, 400; salmon, 75; klim, 25 . . .	100	12.8	797	4.9	0.47	1.95	23.5	46	1.3
Liver residue§	100	13.1	819	5.6	0.46	2.21	21.5	47	14.9
Liver residue§	100	13.4	786	5.9	0.52	2.24	22.3	50	28.4
Bread, 400; salmon, 75; klim, 25 . . .	100	13.4	752	4.8	0.44	2.08	20.3	42	1.3
Bread, 400; salmon, 75; klim, 25 . . .	100	13.1	768	5.3	0.44	2.22	21.1	47	1.4

* Bread, 325; salmon, 100; klim, 25.

** Bread, 250.

† Bread, 350; salmon, 100; klim, 25.

‡ Bread, 400; salmon, 75; klim, 25.

§ Bread, 300; salmon, 75; klim, 25.

Standard bread, canned salmon and klim fed daily as indicated.

Hemoglobin, per cent.

Hemoglobin index = $\frac{\text{Hemoglobin, per cent.}}{\text{Red-cell hematocrit, per cent.}}$

In Table 211 we find that the average output of new hemoglobin per two-week period due to this secondary anemia fraction in 300 gm.

liver equivalent daily, amounts to 72 gm. hemoglobin. This is to be compared with the 90 to 100 gm. hemoglobin base line for whole liver. When the intake of this liver fraction is doubled or tripled or increased even ten-fold, we note but little further increase. We have not yet sufficient evidence to establish these hemoglobin output levels for larger intake with the same security as for the 300 gm. equivalent. No clinical disturbance was noted when these large doses of this secondary anemia liver fraction were fed.

Table 212 shows a continuous series of experiments with whole liver and liver fractions in the same standard anemic dog. All conditions are uniform in this experiment and the food intake, body weight and blood-plasma volume remain constant. If we figure the grams hemoglobin produced by this dog per two-week feeding period (see Methods) we record the following amounts: Secondary anemia liver fraction (W 574) produces 77 gm. hemoglobin per two weeks. Whole pig liver produces 87 gm. hemoglobin per two weeks. Secondary anemia liver fraction (W 608-B) produces 69 gm. hemoglobin per two weeks. Pernicious anemia liver fraction (W 608-C) produces 24 gm. hemoglobin per two weeks. Liver residue (W 608-A) produces 39 gm. hemoglobin per two weeks. These last three fractions were made from a single lot of liver as the numerals indicate.

From time to time we notice that there are slight differences in reaction to liver feeding which we are forced to attribute to a varying liver content of this secondary anemia factor. We cannot explain this at present, but suggest that such changes may be observed and later found to be due to the diet intake preceding slaughter of the pigs.

Table 212 shows a significant change in the color and hemoglobin indices when we compare the feeding of whole liver or secondary anemia fractions with the pernicious anemia fraction feeding. The indices are higher in the former and lower during and after the pernicious anemia fraction ingestion. This may indicate that the secondary anemia fraction facilitates more hemoglobin and less stroma production and the reverse for the pernicious anemia fraction.

Table 213 shows the effect of the secondary anemia liver fraction given in the average dose, in double and in ten-fold dosage. We must keep in mind that this dog (24-45) regularly produces more hemoglobin per week than the average dog, no matter what diet is given. This is an individual peculiarity of this dog which is constant year after year which may mean a larger mass of bone marrow or a more efficient liver-marrow machine. We believe there is much evidence that the liver does much of the preliminary construction of hemoglobin factors or a "pigment complex" which is a parent substance of hemoglobin suitable for the finishing touches within the bone marrow.

TABLE 213. — SECONDARY ANEMIA FRACTION IN AVERAGE AND LARGE DOSES.

Dog 24-45, BULL, FEMALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, bled, gm.
Bread, 400; salmon, 75	100	20.4	1234	4.6	0.52	2.38	20.3	48	1.4
Liver fraction, 300 equivalent*	100	20.5	1136	6.1	0.57	2.50	24.5	61	37.2
Liver fraction, 300 equivalent*	100	20.4	1146	6.2	0.62	2.38	26.1	62	26.5
Bread, 400; salmon, 75	100	20.4	1180	4.4	0.60	2.48	21.5	53	15.4
Bread, 400; salmon, 100	100	21.2	1195	3.9	0.53	2.29	17.9	41	1.2
Liver fraction, 600 equivalent†	100	21.3	1197	4.3	0.56	2.29	21.0	48	1.5
Liver fraction, 600 equivalent†	100	21.3	1106	6.5	0.55	2.36	25.9	61	39.7
Bread, 400; salmon, 100	100	21.5	998	5.8	0.53	2.42	24.7	60	15.1
Bread, 400; salmon, 100	100	21.5	1211	5.1	0.60	2.38	23.4	56	29.2
Bread, 400; salmon, 100	100	21.6	1120	4.4	0.60	2.29	20.7	47	13.8
Bread, 400; salmon, 100	100	21.3	1033	3.9	0.65	2.42	19.6	47	12.3
Bread, 400; salmon, 100	100	21.4	1172	4.5	0.53	2.36	20.4	48	1.6
Bread, 400; salmon, 75	100	19.9	1221	4.4	0.48	2.21	19.1	42	1.2
Liver fraction, 3000 equivalent‡	100	19.8	1128	4.8	0.54	2.21	22.5	50	13.7
Liver fraction, 3000 equivalent‡	100	20.1	1182	5.5	0.55	2.27	24.5	56	31.1
Bread, 400; salmon, 75	100	20.1	1165	5.3	0.57	2.29	22.7	52	35.1
Bread, 400; salmon, 75	100	20.0	1127	4.9	0.58	2.33	20.9	49	27.0
Bread, 400; salmon, 75	100	19.8	1116	3.9	0.59	2.40	19.2	46	1.4
Bread, 400; salmon, 75	100	19.8	1257	4.5	0.57	2.32	21.5	50	14.6
Bread, 400; salmon, 75	100	19.6	1222	4.3	0.51	2.27	19.2	44	1.3

* Bread, 400; salmon, 75.

† Bread, 400; salmon, 100.

‡ Bread, 300; salmon, 75.

Standard bread and canned salmon fed daily as indicated.

Double the usual liver fraction intake or 600 gm. equivalent of whole liver daily for two weeks causes a large hemoglobin output or 107 gm. hemoglobin. When ten times the usual amount of this secondary anemia extract is given or 3000 gm. equivalent daily, we observe no increase in the hemoglobin output or 112 gm. hemoglobin per two-week period. Evidently the dog can make effective use of no large surplus of this liver fraction. Other similar experiments are given in Table 211 to show that there may be a moderate increase in hemoglobin production as we increase the intake of the secondary anemia liver fraction from the standard dose of 300 gm. equivalent daily to 600 gm. equivalent. Beyond this point large excess intake will not push up appreciably the hemoglobin output per two-week period.

The 300 gm. equivalent of this secondary anemia liver fraction is not finally established for Dog 24-45 in Table 213 but from average

values and other data on this dog we feel confident that the output will average about 85 gm. hemoglobin per two-week period.

TABLE 214.—VARIOUS LIVER FRACTIONS GIVEN IN 400 GRAM EQUIVALENT DAILY.

Dog 24-26. BULL, MALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B.C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, bled, gm.
Bread, 250; salmon, 100; klim, 25 . .	100	10.5	688	3.4	0.56	2.27	16.9	38	1.2
Liver fraction, secondary anemia* . .	100	10.9	638	4.6	0.58	2.44	25.1	61	13.6
Liver fraction, secondary anemia* . .	100	10.9	661	5.0	0.55	2.42	23.4	57	16.2
Bread, 250; salmon, 100; klim, 25 . .	100	10.7	638	5.0	0.57	2.42	24.6	59	13.3
Bread, 250; salmon, 100; klim, 25 . .	100	10.6	652	4.3	0.56	2.27	21.1	48	1.5
Liver fraction, secondary anemia, D** .	100	10.6	621	5.2	0.57	2.36	18.0	43	22.2
Liver fraction, secondary anemia, D** .	100	10.8	672	3.8	0.51	2.24	17.4	39	1.2
Bread, 250; salmon, 75; klim, 25 . .	100	10.5	656	4.1	0.49	2.21	18.3	40	1.3
Bread, 250; salmon, 75; klim, 25 . .	100	10.5	700	4.6	0.49	2.29	19.7	45	1.4
Liver fraction, secondary anemia, B† .	95	10.5	627	4.8	0.56	2.32	25.9	60	12.8
Liver fraction, secondary anemia, B† .	100	10.2	616	5.1	0.61	2.36	17.4	41	25.8
Bread, 250; salmon, 100; klim, 25 . .	100	10.2	644	3.2	0.72	2.34	19.8	46	1.3
Bread, 250; salmon, 100; klim, 25 . .	100	10.4	646	3.7	0.62	2.42	18.9	46	1.5
Liver fraction, pernicious anemia, C§ .	100	10.4	626	4.6	0.62	2.19	17.4	38	15.9
Liver fraction, pernicious anemia, C§ .	100	10.7	687	4.0	0.41	2.22	15.0	33	1.1
Bread, 250; salmon, 100; klim, 25 . .	72	10.2	638	5.0	0.48	2.27	21.3	48	1.5
Bread, 250; salmon, 100; klim, 25 . .	81	10.3	622	4.8	0.51	2.27	21.5	49	1.5

* Bread, 250; salmon, 100; klim, 25.

** Bread, 250; salmon, 100; klim, 25.

† Bread, 225; salmon, 75; klim, 25.

‡ Bread, 175; salmon, 75; klim, 40.

§ Bread, 250; salmon, 100; klim, 25.

Standard bread, canned salmon and klim fed daily as indicated.

Table 214 like Table 212 shows a continuous experimental period on the same dog during which time a number of liver fractions were standardized. This dog during this period was suffering from extensive generalized pyorrhea which undoubtedly is in part responsible for the generally low hemoglobin output figures observed. This dog's standard *base line* for equivalent amounts of whole liver feeding during two-week periods amounts to approximately 60 gm. hemoglobin. With this level we may compare the various fractions as given in Table 214. The first liver fraction (secondary anemia) causes an increased hemoglobin production per two-week period of 47 gm. The next liver fraction, D, is a subfraction and is obtained by methyl alcohol extraction of the secondary anemia fraction. We note only a small increase in blood hemoglobin, which amounts

to but 15 gm. and indicates that a large amount of the potent material is not soluble in methyl alcohol. The third liver fraction, B, is the usual secondary anemia fraction made from the same batch of whole liver as D and C. This fraction (B) is a little less potent than the one used in the first part of this table and shows a hemoglobin increase of 34 gm. above the standard base line of control-bread periods. The last fraction, C, is the usual pernicious anemia fraction corresponding to Liver Extract 343 N.N.R. and it as usual shows but little of the liver potency active in secondary anemia. The hemoglobin output per two-week period is but 15 gm. The intake in all experiments is in 400 gm. equivalents obtained from whole pig liver.

TABLE 215.—SECONDARY ANEMIA FRACTIONS SUPPLEMENTED WITH WHOLE LIVER.

DOG 24-2, BULL, MALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, gm.
Bread, 350; salmon, 75; klim, 30 . .	85	15.5	997	3.4	0.59	2.22	17.8	40	1.2
Liver fraction, 300 + liver 110* . . .	100	15.5	984	4.7	0.56	2.31	26.6	61	15.2
Liver fraction, 300 + liver 110* . . .	100	15.4	906	6.2	0.59	2.46	21.9	54	52.0
Bread, 375; salmon, 75; klim, 25 . .	100	15.9	990	4.2	0.61	2.46	20.8	51	13.5
Bread, 375; salmon, 75; klim, 25 . .	71	14.8	952	3.6	0.64	2.40	19.3	46	1.5

DOG 25-23, BULL, MALE, ADULT.

Bread, 350; salmon, 75; klim, 25 . .	92	15.7	921	2.6	0.58	2.03	14.7	30	0.8
Liver fraction, 300 + liver 110* . . .	100	14.7	814	4.0	0.80	2.27	32.6	74	15.8
Liver fraction, 300 + liver 110* . . .	100	15.5	754	4.4	0.93	2.44	25.2	62	50.4
Bread, 375; salmon, 75; klim, 25 . .	100	15.4	853	3.8	0.79	2.48	18.0	45	24.6
Bread, 375; salmon, 75; klim, 25 . .	100	15.8	900	2.9	0.90	2.40	18.9	45	12.2
Bread, 375; salmon, 75; klim, 25 . .	100	15.5	951	3.3	0.67	2.34	18.9	44	1.5

DOG 24-26, BULL, MALE, ADULT.

Bread, 275; salmon, 75; klim, 30 . .	73	9.9	618	3.5	0.63	2.31	19.2	44	1.2
Liver fraction, 300 + liver 110† . . .	97	10.2	597	4.6	0.61	2.46	24.3	60	15.8
Liver fraction, 300 + liver 110‡ . . .	100	10.2	606	5.2	0.66	2.50	18.4	46	44.2
Bread, 275; salmon, 75; klim, 25 . .	100	10.2	618	3.6	0.64	2.50	18.4	46	1.5
Bread, 275; salmon, 75; klim, 25 . .	89	10.4	668	4.9	0.60	2.31	18.7	43	14.4
Bread, 250; salmon, 100; klim, 25 . .	98	10.4	691	3.0	0.55	2.27	14.6	33	1.0

* Bread, 300; klim, 25.

† Bread, 275; klim, 25.

‡ Bread, 225; klim, 25.

Hemoglobin index = $\frac{\text{Hemoglobin, per cent}}{\text{Red-cell hematocrit, per cent}}$

Table 214 like Table 212 also shows an interesting change in the color and hemoglobin indices. During the feeding periods of the secondary anemia fraction, the color and hemoglobin indices are somewhat higher than normal and during and after the feeding of the pernicious anemia fraction we observe somewhat lower figures for the color and hemoglobin indices. This may indicate that the secondary anemia liver fraction is somewhat more favorable for hemoglobin production and the pernicious anemia fraction more favorable for red-cell stroma production.

Table 215 shows the result of supplementing the secondary anemia fraction with small amounts of whole pig liver. The liver fraction is given in 300 gm. equivalent + 110 gm. whole fresh liver equivalent. The mixture is fed daily for the two-week period. The results are somewhat irregular and are not conclusive. The first experiment Dog 24-2, Table 215, shows an output of 80 gm. hemoglobin per two-week period of liver extract and whole-liver feeding. This same dog on secondary anemia liver fraction of 300 gm. equivalent (see Table 211) shows an output of 88 gm. under similar conditions. This would indicate no supplementary effect of the whole liver.

The next experiment—Dog 25-23, Table 215—shows a very different result and the combined liver fraction plus whole liver gives a high output of new hemoglobin of 108 gm. per two weeks. This same dog (Table 211) shows a low output on the secondary anemia liver fraction alone amounting to but 43 gm. hemoglobin per two weeks. This would indicate a very significant supplementary effect due to the whole liver.

The last experiment—Dog 24-26, Table 215—shows a similar result to the preceding. The combined liver fraction plus whole liver gives an output of 58 gm. hemoglobin per two weeks which is distinctly above the low output observed in this dog during the feeding of the secondary anemia fraction alone—40± gm. hemoglobin per two-week period. This conflicting evidence leaves us in some uncertainty about the value of a small supplementary feeding of whole liver added to the dosage of the secondary anemia fraction. These observations are not unlike those obtained in earlier experiments³ with a pernicious anemia fraction (Liver Extract 343 N.N.R.). We suggested that whole liver in small doses might add to the potency of the liver fraction (343) as measured by the new formed hemoglobin in secondary anemia in dogs.

We have evidence that supplementing the secondary anemia liver extract with small amounts of whole kidney will likewise show a supplementary effect. We hope to report soon a series of experiments with a secondary anemia fraction obtained from kidney tissue.

Table 216 gives some evidence that iron and this secondary anemia fraction of liver may supplement each other and give hemoglobin

production values above the average figures for the liver fraction alone. Dog 24-2, Table 216, shows a large hemoglobin output as a result of a two-week daily optimum intake of ferric citrate (Fe 40 mg.) and the secondary anemia liver fraction (300 gm. equivalent). This figures out as 91 gm. hemoglobin production. We may compare this with an experiment (Table 211) on the same dog where the liver fraction alone gave a hemoglobin output of 88 gm. per two-week period. Obviously there is no evidence here for a favorable reaction to the iron intake but the evidence is positive in the last two experiments.

TABLE 216.—SECONDARY ANEMIA LIVER FRACTION + IRON.

Dog 24-2, BULL, MALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, bled, gm.
Bread, 350; salmon, 75; klim, 25 . . .	100	16.1	973	4.1	0.52	2.24	19.2	43	1.1
Liver fraction + iron*	100	15.6	864	5.6	0.54	2.29	32.6	75	33.7
Liver fraction + iron*	100	15.6	878	5.7	0.62	2.40	20.6	49	53.4
Bread, 375; salmon, 75; klim, 25 . . .	100	15.4	853	5.0	0.52	2.40	17.6	42	14.3
Bread, 375; salmon, 75; klim, 25 . . .	100	15.6	945	3.9	0.55	2.36	18.5	43	1.3
Bread, 350; salmon, 75; klim, 30 . . .	85	15.5	997	3.4	0.50	2.22	17.8	40	1.2

Dog 27-241, COACH, FEMALE, ADULT.

Bread, 400; salmon, 75; klim, 25 . . .	100	13.1	768	5.3	0.44	2.22	21.1	47	1.4
Liver fraction + iron†	100	13.3	710	6.7	0.52	2.26	29.9	67	41.3
Liver fraction + iron†	100	13.4	705	6.2	0.59	2.46	26.3	65	47.1
Bread, 400; salmon, 75; klim, 25 . . .	100	13.5	730	5.1	0.57	2.40	20.0	48	28.8
Bread, 400; salmon, 75; klim, 25 . . .	100	13.5	727	4.3	0.53	2.27	20.4	46	1.3

Dog 24-26, BULL, MALE, ADULT.

Bread, 275; salmon, 100; klim, 30 . . .	100	10.1	638	3.6	0.61	2.46	18.7	46	1.3
Liver fraction + iron‡	100	10.3	612	4.7	0.61	2.31	21.5	50	23.7
Liver fraction + iron‡	100	10.4	631	4.6	0.63	2.42	22.2	54	28.1
Bread, 275; salmon, 75; klim, 30 . . .	98	10.4	617	3.9	0.67	2.50	20.5	51	12.6
Bread, 275; salmon, 75; klim, 30 . . .	97	10.3	615	4.2	0.62	2.34	16.5	39	11.6
Bread, 275; salmon, 75; klim, 30 . . .	73	9.9	618	3.5	0.63	2.31	19.2	44	1.2

* Liver fraction, 300 grams equivalent; bread, 350; salmon, 75; klim, 25; given daily.

† Liver fraction, 300 grams equivalent; bread, 400; salmon, 75; klim, 25; given daily.

‡ Liver fraction, 400 grams equivalent; bread, 275; salmon, 100; klim, 25; given daily. Iron, 40 mg., daily given in food as ferric citrate.

Dog 27-241, Table 216, gives convincing evidence that the iron salt and the liver fraction do supplement each other. This dog on the liver fraction alone (Table 211) shows a hemoglobin output of

69 to 77 gm. per two-week period. When we supplement this intake of the secondary anemia liver fraction (300 gm. equivalent daily) with ferric citrate (40 mg. Fe daily) we observe a high total hemoglobin output of 110 gm. per two-week feeding.

Dog 24-26, Table 216, also gives similar evidence that an iron salt and this liver fraction supplement each other. This dog (Table 211) on an intake of the secondary anemia liver fraction (400 gm. equivalent daily) shows a hemoglobin output of about 40 gm. hemoglobin. When the same dose of this liver fraction is fed plus ferric citrate (40 mg. Fe daily) we note a definite rise in hemoglobin output amounting to 65 gm. hemoglobin per two-week feeding.

TABLE 217.—SECONDARY ANEMIA LIVER FRACTION—ASHED.

Dog 27-241, COACH, FEMALE, ADULT.

Diet periods, 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hematocrit, per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed, bled, gm.
Bread, 400; salmon, 75; klim, 25 . . .	100	13.5	727	4.3	0.53	2.27	20.4	46	1.3
Liver fraction, ashed*	100	13.6	722	5.4	0.59	2.24	25.0	56	35.2
Liver fraction, ashed*	100	14.1	752	4.8	0.55	2.38	23.1	55	18.1
Bread, 400; salmon, 75; klim, 25 . . .	100	14.1	845	5.8	0.57	2.19	17.1	37	29.2
Bread, 400; salmon, 75; klim, 25 . . .	100	14.4	820	4.1	0.51	2.26	18.7	42	1.2

Dog 24-45, BULL, FEMALE, ADULT.

Bread, 400; salmon, 75	100	19.6	1222	4.3	0.51	2.27	19.2	44	1.3
Liver fraction, ashed†	100	19.8	1216	3.9	0.55	2.31	18.7	43	1.3
Liver fraction, ashed†	100	19.8	1116	5.4	0.59	2.31	25.0	58	37.4
Bread, 400; salmon, 75	100	20.0	1160	4.9	0.52	2.31	22.8	53	13.9
Bread, 400; salmon, 75	100	19.9	1151	4.7	0.56	2.42	20.5	50	15.0
Bread, 400; salmon, 75	100	20.2	1189	4.7	0.51	2.46	17.9	44	11.8
Bread, 400; salmon, 75	100	20.4	1234	4.6	0.52	2.38	20.3	48	1.4

Dog 24-25, BULL, MALE, ADULT.

Bread, 350; salmon, 75; klim, 25 . . .	100	14.3	923	3.1	0.76	2.50	18.8	47	1.3
Liver fraction, ashed‡	100	14.8	868	3.5	0.66	2.42	19.2	46	1.4
Liver fraction, ashed‡	100	14.0	862	5.5	0.64	2.29	19.1	44	36.1
Bread, 400; salmon, 75; klim, 25 . . .	100	14.2	870	4.5	0.62	2.34	17.9	42	13.7
Bread, 400; salmon, 75; klim, 25 . . .	97	13.9	927	3.6	0.61	.42	8.0	44	1.3

Liver fraction ash given in 300 gm. equivalent daily.

* Bread, 400; salmon, 75; klim, 25; daily diet.

† Bread, 400; salmon, 75; daily diet.

‡ Bread, 350; salmon, 75; klim, 25; daily diet.

Table 217 gives interesting information about the ash of this secondary anemia fraction. We may recall that an optimum iron

salt intake may show an average hemoglobin output per two-week feeding of 50 gm. These ash experiments show average values of 60 gm. hemoglobin produced per two-week feeding, when the ash from 300 gm. equivalent of this secondary anemia fraction is given. The optimum iron intake¹⁰ is 40 mg. daily and this ash as fed contains 10 mg. iron as metal per 300 gm. equivalent, so that other salts would seem to be concerned.

This ash gives very similar results when compared with the ash from whole liver¹ although the ashing methods are somewhat different. The ash obtained from whole liver was subjected to a more destructive process which may have burned off some salts not destroyed by the muffle method used on this secondary anemia liver fraction which was ashed. This may explain why the ash of this liver fraction runs a little higher than whole-liver ash as measured by hemoglobin production in anemic dogs.

Discussion. Does liver therapy benefit human cases of secondary anemia? This is not the place to review the considerable mass of clinical papers which are accumulating rapidly because of a developing inquiry in this field. Reports for and against liver therapy are numerous. We believe in many of the negative reports that the liver feeding was inadequate in amount and duration. Possibly the reason for this may be outlined somewhat as follows: Liver therapy in pernicious anemia is spectacular and results are obvious within two weeks, with large production of new red cells and a rapid rise in blood hemoglobin. By contrast the reaction in secondary anemia is less striking and may be delayed. There are facts which explain these differences and it may be worth reviewing them briefly at this time.

Pernicious anemia is a disease in which there is a great surplus of hemoglobin pigment and related pigments. The red cells are saturated with the maximum content of hemoglobin. The muscle hemoglobin is high in spite of anemia and inactivity, which tend to lower the muscle hemoglobin level. The blood serum and body fluids contain an excess of pigments related to the blood hemoglobin. The urine and feces contain an excess of pigment which is related to blood hemoglobin. On the basis of the pathologic findings in the blood, bone marrow and organs, Whipple^{5,6} several years ago proposed an explanation for these findings in pernicious anemia, *not* on the basis of red-cell *destruction*, but on the basis of faulty *construction* or the lack of red-cell stroma constituents. This explanation fits in with the observed facts to date and gives a ready explanation for the spectacular regeneration of red cells in pernicious anemia following liver feeding. We may assume that the liver feeding supplies the missing element necessary for maturation of the red-cell stroma, that large reserves of pigment building materials as well as pigment are stored in the body and the red cells are then produced in extraordinary members.

Secondary anemia in direct contrast to pernicious anemia is a disease in which there is a *deficit* of hemoglobin pigment and related pigments. The red cells are lacking in normal content of hemoglobin and consequently there is a relative excess of stroma. The body pigments are subnormal in concentration and there are no excess pigment derivatives unless active red-cell destruction is in progress. Evidently the normal blood-forming organs under the stimulus of a low blood-hemoglobin level can produce stroma more actively than new hemoglobin. The reserves of parent hemoglobin material or building stones suitable for new hemoglobin fabrication are exhausted or reduced and can be restored only through food intake—organic and inorganic. We have experimental evidence to be published soon that infection and intoxication can delay the new hemoglobin production in normal hyperplastic bone marrow in dogs.

All these facts suggest why the reaction to liver therapy is bound to be less spectacular in secondary anemia than in pernicious anemia but do not lessen the importance of liver therapy in secondary anemia. It has been proved beyond a reasonable doubt that liver and kidney in the diet furnish the maximum supply of substances most suitable for new red-cell and hemoglobin fabrication. It is not always easy for an anemic patient to take the required amount of liver or kidney. This secondary anemia liver fraction described above may be of service in certain cases of this type.

Iron must be mentioned in any discussion of secondary anemia but need not be reviewed in detail as this has been done very recently.¹⁰ It may be stated that the optimum intake of iron from salts and food has been established for the dog in experimental anemia as about 60 mg. iron as metal daily. Above this level of intake a large excess of iron salts gives no further rise in the production of hemoglobin. It appears to make no difference whether iron is given as ferrous chlorid, ferric citrate, ferrous carbonate, ferrous sulphate or ferrous ammonium sulphate. The optimum total intake of iron exceeds three-fold the loss of iron by bleeding and wastage of red cells. It is obvious that this iron has some effect in the body other than that of mere replacement of iron in the lost or worn-out hemoglobin. This iron in excess of hemoglobin iron requirements obviously exerts some influence upon internal body metabolism so that more hemoglobin is produced. We may call this a salt effect and it is probably similar to the effect noted with feeding salt mixtures, copper and other metals, and ash from liver and kidney.

Summary. A liver fraction is described which contains 65 to 75 per cent the potency of whole liver for new hemoglobin production in experimental anemia due to hemorrhage. This fraction represents 3 per cent of the weight of the whole liver.

Probably a number of active substances are represented in this liver fraction. Inorganic substances are important.

Supplementing this liver fraction with iron may increase the total output of hemoglobin. The same thing is true for whole liver feeding plus iron which may give maximal hemoglobin production in experimental anemia.

Supplementing this liver fraction with small amounts of whole liver may increase the total output of new hemoglobin above the level due to liver fraction alone.

These experimental observations will be of greater interest when compared with similar controlled observations in various human secondary anemias.

This liver fraction is palatable and can be taken in considerable amounts without clinical disturbance.

Reasons are given why liver therapy is so spectacular in pernicious anemia and notably less effective in certain secondary anemias.

We urge that liver therapy should not be considered inert in any type of secondary anemia until it has been given a thorough test.

All evidence available points to liver and kidney as supplying the essential factors in most available form for the reconstruction of new hemoglobin and red cells in anemia.

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RHINAL MYIASIS.

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RHINAL myiasis, nasal myiasis, or myiasis narium, the infestation of the nasal cavity with fly larvae, is said to be of fairly common occurrence in certain countries of Asia and Africa, as well as in tropical and subtropical portions of America. In North India, where the condition is reported to be especially frequent, it is known

as "peenash," and many cases are far advanced before medical aid is sought. According to one writer, screw-worm myiasis is common in the Americas from the Argentine to Canada, but Blain questions this assertion in so far as it applies to the states of Pennsylvania and Michigan. Stitt observes that the screw-worm fly is common over nearly all of North and South America. Cases of human nasal myiasis have been reported from Arizona, Iowa, Kansas, southern California, New Mexico, Texas and probably from other states in this country, but the literature on the subject is by no means voluminous. Blain, referring to myiasis in general, states that "the disease is probably far more common in man than is generally supposed." Yount and Sudler collected reports of 23 cases occurring in Arizona in the course of one season. Sporadic instances are apt to occur wherever the screw-worm fly is prevalent; however, in the United States the incidence of the nasal form of the disease is not sufficiently large to deprive the occasional case of interest, and for that reason 2 case reports are presented with this article.

Etiology. In the New World, human myiasis is produced by several different species of flies. The common screw-worm fly, *Chrysomya macellaria*, is the usual offender in this region. This is a dipterous insect of the suborder Cyclorrhapha. It is distinguished from the ordinary blue-bottle fly by the presence of three longitudinal black stripes arranged symmetrically on the thorax or scutum. It is a small fly about 1 cm. to $\frac{1}{2}$ inch in length. The head is short, of a red or yellow color and is closely attached to the body, which latter is covered with stiff black hairs and presents a bluish or greenish metallic appearance. The female lays from 200 to 300 eggs or more. These eggs hatch in a few hours when deposited in a favorable environment. The larvæ are described as "whitish, footless grubs, rather slender and quite active." They reach maturity in five to six days, at which time they are from $\frac{1}{2}$ to $\frac{3}{4}$ inch long. They have twelve segments with a belt of minute spines or bristles around each segment. They are largest near the posterior end, tapering almost to a point at the head, thus somewhat resembling a screw, from which is derived their name. On reaching maturity they drop to the ground and there, burying themselves, pass through the pupal stage to develop into the adult fly. The pupæ are brown, elongated oval in shape and about 1 cm. long. The pupa stage occupies from nine to twelve days, but varies somewhat and may be as long as fourteen days. Thus, the metamorphoses involved in the development from egg to adult fly extend over a period of two to three weeks, so that a number of generations may be bred in a single season. In rhinal myiasis the larvæ occur in the nose as facultative parasites, and from there invade the surrounding tissues, the paranasal sinuses or even penetrate the bone. Other diptera of the same family may cause the disease, notably *Calliphora vomitoria* and *Lucilia cæsar*; sometimes also members

of the related family Sarcophagidæ may be responsible for the condition. In short, a number of different genera of flies have been indicted as the causative agents of myiasis narium.

The exciting cause of the disease is, of course, the larvæ themselves, but aside from this, several predisposing or contributory factors may be mentioned in considering the etiology. The most important of these seems to be the presence of preëxisting pathologic conditions of the nose. In both cases here reported there was an antecedent chronic nasal disease; in 1 case of undetermined, but probably luetic, character; in the other, an atrophic rhinitis. Such factors have been present in other reported cases. Dixon's case had had a slight epistaxis the day preceding that on which the fly entered his nose. McColloch reports 2 cases from Laredo, Texas, in both of which there was chronic atrophic rhinitis. Ozena seems to present an especially inviting field for ovipositing to some species of flies, and it is thought that the offensive odor attracts them, likewise after epistaxis the smell of blood guides the fly to the unfortunate victim. Yount believes that chronic rhinitis or even uncleanness predisposes to the disease. Among predisposing affections noted are also chronic nasal catarrh, epithelioma and luetic rhinitis; the presence of the disease itself invites reinfection.

Sleeping in the open affords the fly an opportunity to deposit its eggs undisturbed, and hence is of great importance as a contributory cause. McColloch's 2 cases and my first case were infected in this way. Yount and Sudler also describe 2 cases similarly infected, 1 in a morphin habitué, the other in an alcoholic during a drunken debauch.

The climate and season of the year, inasmuch as they affect the habits of the flies which cause the disease, also affect its prevalence. The seasonal incidence varies with the latitude, as the flies are not active during cold weather, hence in the northern hemisphere cases are apt to occur earlier in the year as we approach the equator. We should also expect to find a larger number of cases in the warmer climates, where the flies have longer periods of activity and are more numerous, and, judging from available data, this is the true state of affairs. The disease occurs in both sexes, but is more frequent in the male, whose habits of life expose him more often to the infection. For the same reason, the disease is commoner in the country than in the cities, and is seen more often in the poor than among the well-to-do. It occurs most often in farmers and others whose occupation consists of open-air work in the rural districts.

In studying an active case there is usually obtainable a history of a fly in the nose two or three days before the onset of symptoms. When the patient is not seen until the disease is well developed, he may be in such a condition as to preclude the possibility of securing any history at all unless the relatives or friends can supply the missing data. In one case the dead fly was blown from the nostril

several days after the onset of symptoms, and since the patient was asleep when the fly entered, he had no knowledge of its presence. The eggs in the favorable environment in which they are deposited hatch out in twenty-four hours or less, but the movements of the larvæ may not be perceived by the patient. The young parasites migrate farther up into the nasal cavity, feeding on the discharge present from antecedent causes or due to the irritation caused by their presence. Patton maintains that the larvæ can imbibe only fluids, but that their toxic salivary secretion in conjunction with the inevitable secondary bacterial infection breaks down the tissues of the host, although the worms themselves cannot feed directly on the tissues. He further states that they are unable to make their way through bone, and hence cannot enter the brain; but this contention is at variance with the statements of other writers. In Snow's case the hyoid bone was destroyed, and the palate bone so greatly damaged that it broke on the slightest pressure. In 1 of the Arizona cases, reported by Dr. Looney, "destruction of the soft and bony tissue was such that one could look from the lower border of the frontal bone directly into the esophagus through an opening $2\frac{1}{2}$ inches wide by $3\frac{1}{2}$ inches long."

Symptomatology. Subjective symptoms are noted in from one to three days from the time the eggs are deposited in the nose, and in both cases here described partial obstruction to breathing on the affected side was the first evidence of the disease noticed by the patient. Sometimes there is first noticed a feeling of discomfort or a peculiar sensation at the root of the nose, radiating outward along the supraorbital ridge. This gradually increases, until it becomes an intense pain, most frequently located over the frontal sinuses, but may perhaps be felt in the maxillary region, the temporal region, or occasionally in the region of the ear. In one instance severe headache persisted for a week after all the larvæ had been removed. Early subjective symptoms are accompanied or soon followed by a serosanguinous nasal discharge which is characterized by a foul odor. The discharge becomes more profuse and appears also, but in smaller amount, from the other nostril as the disease advances. It then assumes a more purulent aspect, being thicker and of a dirty reddish-brown color, while the odor is so offensive as to be nauseating. Dixon observes that the presence of blood in the discharge indicates the activity of live worms in the tissues. After destruction or removal of the larvæ, as the patient begins to improve, the blood disappears from the discharge, which then becomes mucopurulent or mucoseropurulent and rapidly diminishes in quantity, to disappear finally as convalescence is established.

Coincident with the beginning of the nasal discharge, the patient begins to clear his throat and expectorates frequently or develops a loose cough which brings up a purulent material. Sometimes sneezing is an early symptom. After treatment is instituted, or

even before, the sputum is apt to contain a few living or dead larvæ which have made their way or have been washed by irrigating fluids into the nasopharynx. There is intense irritation in the nose. Pyrexia sets in, the temperature rising to 101° or 102° F. Headache and neuralgia are usually marked, especially on invasion of the sinuses by the parasites. The nose, eyelids and cheeks swell, the swelling arising first and being more pronounced on the affected side, but also involving the opposite side. The irritative eye signs of lachrymation redness, photophobia and blepharospasm develop, the bulbar and palpebral conjunctivæ are irritated or inflamed and mucopurulent material gathers at the inner canthi. Subjective sensation of activity within the nasal chambers has developed by this time and the swarming larvæ can be seen in active motion. The number of larvæ varies from a score or more up to several hundred. As the disease advances, the surface over the swelling becomes discolored, resembling erysipelas in appearance, and the destruction of tissue may even extend to the surface of the face, breaking down the skin to produce a foul open sore. In some cases movement of the larvæ has been discernible under the intact skin. The nasal conchæ may be destroyed, the septum and palate perforated and the parasites not infrequently make their way into the paranasal sinuses, occasionally into the orbit, even entering the bulbus oculi, or, according to some writers, may even invade the intracranial space and the brain, in which event secondary bacterial invasion results in a fatal issue.

The condition of the psyche in the early stages is marked by anxiety and depression. However, as the disease progresses and toxic symptoms develop, apathy supervenes which gradually, in spite of mental irritation at ineffective attempts to clear the nose, deepens into stupor or even into coma. In a case reported by Franchini and in the second case reported here the psyche remained undulled, but there was extreme nervous irritability and restlessness. In some cases there is delirium or a semidelirious state. With the improvement of the condition in the nose, the mental symptoms clear up with remarkable promptness.

Some observers include pallor and loss of weight among the objective symptoms of the disease. Epistaxis may appear in the active stage or may be a late symptom. Barlara reports a case from Argentina, in which the patient succumbed to hemorrhage after apparently having been cured. The hemorrhage in my second case was a delayed symptom, but fortunately did not result fatally.

Diagnosis. The diagnosis is made by observing the larvæ. Early in the disease they may be perceived more easily after shrinking the swollen mucous membrane with cocain and adrenalin, later they are seen without difficulty high in the nasal cavity and still later may make their appearance in the nasal fossæ, be expectorated from the nasopharynx or appear at artificial openings of their own forma-

tion. Before the larvæ are seen, however, their presence may be suspected. Especially in the warmer climates, a patient developing nasal obstruction, foul nasal sanguinopurulent discharge and intense irritation in the nose should be suspected of having nasal myiasis; a history of a fly in the nose several days before makes the diagnosis almost certain. Few conditions are apt to be confused with that under discussion. When the first symptoms appear the presence of an intranasal foreign body might be hypothecated by the observer, or perhaps local inflammatory swelling from some other cause might be considered as a possible diagnosis. However, even at this stage of the disease, the larvæ may be made out if the nasal cavity is carefully inspected with a good light. If they are still unseen, chloroform may be successful in bringing them to view.

After the disease is fully developed it may present the appearance of erysipelas, anthrax, acute paranasal sinusitis, cellulitis of the face or noma; but there should be no difficulty in making the correct diagnosis at this time as the larvæ are readily observed.

Complications. Complications in the main are due to extension of the destructive process into adjacent structures, together with the migration of the larvæ into the surrounding tissues or sinuses. Perhaps the commonest of all complications is paranasal sinusitis, and of the sinuses the frontal seems to be the one most frequently involved. Otitis media with suppuration was reported in one of the Arizona cases. Migration of the larvæ into the orbit or into the cranial cavity has already been mentioned. Hemorrhage may occur in serious or even fatal proportions. Gastric and intestinal myiasis may rarely be complications or sequelæ. Inspiration pneumonia is occasionally met with. General sepsis and septic meningitis are said to be encountered, but seem to be rare, as infrequent mention of them is made in the literature.

Prognosis. The seriousness of the disease is indicated by the report of Yount and Sudler of a series of 23 cases of myiasis, with a mortality of 22 per cent in 18 nasal cases. The prognosis is governed largely by the severity of the symptoms and time of beginning treatment. Where but a few larvæ are present the outlook is more favorable. Preëxisting diseases, such as chronic nephritis or organic heart trouble may determine a fatal issue. As the larvæ mature in a few days the period of disability is relatively short, unless prolonged by complications, reinfections or sequelæ. Death may occur from exhaustion, hemorrhage, sepsis, meningitis or pneumonia. If the patient escapes a fatal termination, varying degrees of deformity may result from tissue destruction—saddle nose, perforated septum, perforated palate or destruction of portions of the nose or cheek may occur. Patterson recorded a case which resulted in complete destruction of the nose and part of the face. The conchæ and nasal septum are commonly attacked. When ozena was present before hand, it is apt to be made worse when portions of the mucous

membranes lining the nasal cavities are destroyed. If larvæ enter the eyeball, loss of the eye may result. Franchini reports a case where spontaneous recovery took place, but was followed by intestinal myiasis.

Treatment. Treatment may be divided into preventive or prophylactic and active. Of great importance in the prevention of the disease is the treatment and where possible the cure of any intra-nasal pathology. In cases of ozena or other conditions which may not be entirely eradicable, or which tend to recur, the patient should be warned of the danger of myiasis. He should also be cautioned against sleeping in the open unscreened. Where exposure is considered likely the anterior nares may be plugged with cotton wool soaked in antiseptic. Finally, in event a fly enters the nose, the patient should report to a doctor at once for removal of the eggs, in the event any should have been deposited. Approaching the problem from another angle, prevention of breeding of the flies whose larvæ cause the condition may to a great degree be brought about by the proper disposal of refuse and of the carcasses of dead animals.

The active treatment is further divided into curative and symptomatic. The curative treatment consists in the removal of the larvæ and the use of measures to promote healing of the lesions they have caused. Removal of the larvæ is accomplished in part mechanically and in part by the use of drugs. McCulloch reports mechanical extraction of the larvæ at successive sittings at two- or three-hour intervals after chloroform had proved ineffective. Other writers advise the removal of as many larvæ as possible mechanically at one sitting, followed by the use of drugs. A number of drugs have been recommended for this purpose. Jeanselme and Rist advise the injection of pure benzene into the nasal cavities. Turpentine, ether, phenol solution and chloroform are also of value. Stevens states that irrigation with 5 per cent phenol is the best treatment. Chloroform, however, appears to be the more widely used, and is employed in several different manners. The vapor may be inhaled, or as in Dixon's case, pledgets of cotton saturated with undiluted chloroform may be inserted into each nostril. The pledgets were kept saturated and were left in place five minutes. Blain advised chloroform in the strength of from 25 per cent to the pure drug. Stiles advises washing with 20 per cent chloroform in milk or with phenol solution. Patton advises the use of weak chloroform water or the local application of turpentine, and states that the larvæ should not be killed *in situ* as they are then a source of secondary infection. Yount and Sudler obtained their best results by spraying chloroform, 25 per cent to the pure drug, from a syringe with a spray tip "ejecting the chloroform with considerable force up into the nasal chambers and, if possible, their accessory sinuses." Olive oil is used as the diluent. Immediately after spraying the nose

larvæ are searched for and removed with forceps. This procedure is carried out twice a day until all larvæ have been removed. The plan of treatment generally chosen seems to be the use of chloroform in one of the methods described, combined with removal of accessible larvæ with forceps immediately thereafter, this sequence being repeated at intervals varying in length of time with different workers. As an adjuvant line of therapy various bland irrigations have been recommended to promote cleanliness or to allay the stench accompanying the disease. Normal salt solution, boric acid solution, 1 to 4000, potassium permanganate solution or chloroform water may be used as often as indicated.

The symptomatic treatment meets the indications as they arise, and general hygienic measures are enforced. Pain usually requires the use of morphin, but may be amenable to coal-tar preparations or codein. Nervousness, anxiety and insomnia may yield to bromids or other hypnotics. In weakened states stimulative and supportive measures are called for. If the patient's mind is clear the repulsive nature of his malady robs him of any desire of eating, but liquid and semiliquid foods may be well taken. Finally, plastic surgery may be indicated for the correction of deformities resultant from the disease.

Case Reports. CASE I.—J. S., colored, aged seventeen years, of Raywood, Texas, a well-developed, fairly well-nourished French negro of low-grade mentality. When first seen on night of September 25, he lay in the dorsal decubitus in a stuporous condition. The eyelids of the left eye were edematous and the eye was closed by the swelling. The conjunctivæ of both eyes were red and injected and at inner canthus of each a bead of mucopurulent material had gathered. Lachrymation and photophobia were well-developed symptoms. The nose and adjacent portion of the face on each side were also swollen and edematous. The nasal cavities were occluded and breathing was through the mouth, which remained constantly open except when the patient swallowed or expectorated. A foul-smelling sanguinopurulent fluid of dirty reddish-brown color trickled slowly from the nose. Two old perforations of the palate were present and a history of some form of nasal trouble having existed over a long period of time suggested the first diagnostic consideration of chronic syphilitic rhinitis with secondary septic infection. The temperature was 101.4° F. Two days prior to this the nasal cavities had become obstructed, but at that time there was no discharge, and since then the patient's condition had been growing progressively worse. No active movement could be observed inside the nasal cavity, and as far as could be determined, there was no subjective sensation of active movements. Antiluetic treatment was instituted and, in addition, continuous wet dressings to the face and solution of mild silver salt instilled in the eyes and nose at regular intervals.

The following morning the temperature had dropped to 99.6° F., and the patient's general condition appeared slightly improved, although the swelling and edema showed no perceptible change. On September 27, active motion was detected in the nose and the true condition realized. Ether having been successfully employed in treating dermal myiasis, this drug was used for nasal irrigation in 50 per cent solution in olive oil. A few larvæ came out dead with the irrigating fluid, others were removed with tissue forceps afterward, some dead and some alive. Some were embedded

in the tissues and were pulled out with some difficulty. Even the dead ones presented a rasplike resistance to removal due to the spines on the segments. Forty larvæ were removed at this time.

On September 28, edema had increased some, extending further to the left than to the right. The left nostril was distended, being packed tightly with larvæ, evenly arranged and presenting somewhat of a honeycomb appearance in the aggregate. A few larvæ were discerned on the right side. The septum was perforated. Any attempt to remove larvæ with forceps would initiate a rapid scramble of the parasites further up into the nasal cavity. A small fresh perforation of the soft palate was present through which a larva could occasionally be seen. The nose was irrigated with chloroform in milk, the fluid being carried to the upper parts of the cavity by means of a soft rubber catheter. About 25 more larvæ were removed. The same afternoon no living larvæ could be seen. Some dead ones had passed. Some had been swallowed, causing vomiting, but none were observed in the feces and no gastrointestinal symptoms developed. No accurate count of the number had been kept. The patient complained of intense headache over right frontal sinus. Codein and aspirin were given for this with amelioration but without complete relief.

On September 29, considerable swelling of the soft palate with redness and difficult deglutition. Discharge from nose scanty. Edema reduced. Patient brighter and becoming talkative. He stated that on September 26 he blew a dead fly out of his nose, but did not know how long it had been in there. Several days before that he did not remember exactly how many, he had lain down under a tree in the yard for a nap, and probably the fly entered while he was asleep.

Recovery was uneventful, but no follow-up of the case could be made as the patient migrated to Louisiana as soon as he was able to travel.

The larvæ were the typical screw worms and were classified as *Chrysomya macellaria* larvæ.

CASE II.—M. J., white, aged twelve years, of Liberty County, Texas. On October 7, date of first visit, the patient was in bed, very restless, changing position at frequent intervals and, although not complaining of any pain, was evidently experiencing much discomfort. The temperature was 100.8° F. There was a partial obstruction to breathing in the right nostril and from the right anterior naris a drop of brownish serous discharge would emerge at frequent intervals. The patient was making frequent attempts to dislodge the obstruction in his right nostril, stopping left nostril by pressing side of nose with finger and blowing vigorously through the right. Nothing emerged, however, except the discharge previously referred to. There was a slight discharge from the left nostril which was rimmed with dried secretion. There was a collection of purulent material in corner of the right eye, and considerable swelling, most pronounced on right side beside the nose. The loose tissues under the right eye were slightly puffed. There was an offensive musty odor to discharge. The psyche was clear.

On October 1, the boy had been riding through the woods on a truck and a fly flew in his nose. It was there for only a moment, as the patient at once began efforts at dislodgement which were readily effective. On October 4, he blew some hard object from his nose and that evening began to have a little fever. On October 5, the nose began to discharge a sero-sanguinous fluid, and the face began to swell on right side next to nose.

On October 8, temperature was 101° F. The swelling had increased. The right eye was almost closed; the nasal discharge was brighter red and more profuse. On examination, larvæ could be seen moving about high up in the right side of the nose for the first time seven days after the dead fly had been blown out. The nose was irrigated with 20 per cent chloroform

in milk; only four worms were removed. The same fluid was dropped in with a medicine dropper every thirty minutes.

On October 9, temperature was 100° F.; pulse, 76. No worms after 10 A.M. Total worms removed, 169, all but a few of which were dead when expelled. Profuse bright serosanguinous discharge.

On October 10, the patient was up; had no fever. Moderate amount of mucoseropurulent discharge from right nostril. Patient discharged from treatment with directions for after care.

On October 11, a hurry call to see the patient again, who had blown a piece of necrotic tissue about 1 by 2 cm. from nose; copious hemorrhage from left nostril followed. This continued for about one hour, stopping shortly before my arrival. A short while after this the patient blew another larva from the nose. This was said to be somewhat larger than the others and proved to be the last. Total number of larvæ, 170.

On November 15, the nose had healed. Septum deflected to left in lower portion; no perforation seen. Right inferior turbinate almost completely destroyed, a small beadlike projection on outer nasal wall being the only visible remnant. Ozena persists as before intercurrent affliction. The larvæ in this case did not present typical screw-worm appearance, being smoother, rounder and somewhat smaller. Unfortunately, they were not identified.

Summary. 1. While fairly common in some parts of the world, rhinal myiasis is not of frequent occurrence in the United States, though perhaps more so than the number of reported cases would indicate. Two cases are reported herewith.

2. Several different genera of flies have been found to cause the disease. The screw-worm fly, *Chrysomya macellaria*, is, however, most often the causative agent in this region.

3. Antecedent nasal disease is important as a predisposing factor in the development of the condition. Sleeping in the open, un-screened, favors the infestation. Other etiologic influences are dependent on the habits and prevalence of the flies and the frequency of human exposure.

4. The cardinal symptoms are nasal obstruction with foul nasal sanguinopurulent discharge and intense irritation in the nose. Pain is usually present and often severe. Swelling is more marked on the affected side, but involves both sides as the disease progresses. There is moderate elevation of the temperature. Hemorrhage is not unusual and may be a delayed symptom. Tissue destruction is sometimes extensive. Mental symptoms vary from anxiety and restlessness to stupor or coma.

5. The diagnosis is made by observing the larvæ in the nose.

6. Paranasal sinusitis is the most frequent complication. Other complications arise from migration of the larvæ into other structures and from accompanying bacterial infections. Epistaxis may occur in fatal proportions. Inspiration pneumonia may develop or rarely general sepsis or septic meningitis.

7. The prognosis may be guarded due to the high mortality and the frequency of complications. Prognostic criteria which may indicate a more or a less favorable outcome are the general physical condition of the patient, the magnitude of the infection, the stage

of the disease at the time of beginning treatment and the presence or absence of complications.

8. Though a number of different drugs have been advocated in the treatment of rhinal myiasis, the therapeutic procedure generally adopted in this country is the use of chloroform by one of several methods, combined with the mechanical removal of accessible larvæ. Symptomatic treatment meets the indications as they arise.

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ANEMIA IN JAUNDICE.*

I. A CLINICAL STUDY OF CASES IN WHICH JAUNDICE WAS OF OBSTRUCTIVE OR INTRAHEPATIC TYPES.*

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ANEMIA is commonly seen in patients with jaundice that is due to obstruction of the common duct by stone, stricture, carcinoma of the head of the pancreas, or malignant disease of the biliary passages and in patients with jaundice due to intrahepatic causes. The anemia may be moderate or relatively severe and it may occur independently of fever, chills, hemorrhage or other clinical evidences of infection or of loss of blood.

In an effort to throw some light on the etiology of the anemia which occurs in jaundiced patients, a preliminary survey was made of those cases of jaundice observed at the Clinic during the last two and a half years. This survey was undertaken in order to determine the frequency with which anemia occurred in each of the various types of jaundice, the degree of the anemia and the relationship, if any, between the intensity of the anemia and either the duration or the intensity of the jaundice. Our chief interest was in those patients who presented anemia without any clinical evidence of infection or loss of blood. Consequently those with chills, fever, leukocytosis, purpura, melena, hematemesis or hematuria were not included in the present group of cases used for drawing conclusions regarding the relationships of jaundice and anemia. An attempt has also been made to study this type of anemia experimentally in animals, and the results of this work will be reported elsewhere. A group of 347 cases of jaundice was made the basis of the study reviewed here.

Anemia was considered to be present if the value of hemoglobin was below 70 per cent (Dare) and if the erythrocyte count was below 4,000,000 per c.mm. Of this group of 347 cases, 329 were observed during the years 1926 and 1927, and in 90 of the latter anemia was

* The data presented in this paper are taken from a thesis submitted by F. M. Jordan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine, 1929.

present. To this number, 18 selected cases with anemia, observed in 1925, were added, making a total of 108 cases of anemia. In determining the frequency with which anemia occurred, the group of 329 cases observed during 1926 and 1927 was selected, but for the remainder of the data the entire group of 347 cases was selected. The diagnosis was confirmed in most cases by operation or by necropsy. In some cases, including nearly all of those of intrahepatic jaundice, the diagnosis depended on the clinical data, the behavior of the patients while under observation and the subsequent course after they left the hospital.

Carcinoma. In the majority of the patients who had carcinoma the lesion was in the head of the pancreas. The few remaining patients in this group had carcinoma of the gall bladder or biliary ducts, and one or two had biliary obstruction as a result of metastasis of carcinoma of the stomach or colon to the regional lymph nodes. Of the total number of 347 cases of jaundice, there was carcinoma in 81, in 33 of which anemia was present (tabulation). Anemia occurred in 25 of 73 cases observed during 1926 and 1927 (34 per cent). The lowest percentage of hemoglobin was 38, with an average of 56. The lowest erythrocyte count was 2,650,000, with an average of 3,470,000. By comparing the amount of serum bilirubin, the erythrocyte count, the percentage of hemoglobin and the duration of jaundice, curves were constructed to show the correlation between the intensity of the anemia and either the duration or the intensity of jaundice. So far as this group of patients was concerned, there did not appear to be any correlation clinically between the intensity of the anemia and either the duration or intensity of the jaundice (Figs. 1 and 2).

OCURRENCE OF ANEMIA IN PATIENTS WHO HAD JAUNDICE.

Group.	Total cases.	Total cases of anemia.	Cases in 1926-1927.	Cases of anemia in 1926-1927.	Per cent of cases of anemia in 1926-1927.	Average hemoglobin, per cent.	Average erythrocytes (millions).
Carcinoma	81	33	73	25	34.2	55.7	3.47
Intrahepatic jaundice	93	31	90	28	31.1	59.0	3.61
Cholelithiasis	142	30	138	26	19.2	61.0	3.67
Stricture	31	14	28	11	39.3	59.0	3.62
Totals	347	108	329	90			

Intrahepatic Jaundice. All cases of arsphenamin jaundice, catarrhal jaundice and biliary cirrhosis were included under the common heading of intrahepatic jaundice, according to McNee's classification. Of the total number of 347 cases of jaundice, 93 belonged to this group, in 31 of which anemia was present (tabulation). Anemia

occurred in 28 of 90 cases (31 per cent) observed in 1926 and 1927. The lowest erythrocyte count was 2,700,000 and the average count was 3,610,000. The lowest percentage of hemoglobin was 40, with an average of 59. As in the preceding group, there did not appear to be any definite correlation clinically between either the intensity or duration of the jaundice and the anemia occurring in this group of cases (Figs. 1 and 2).

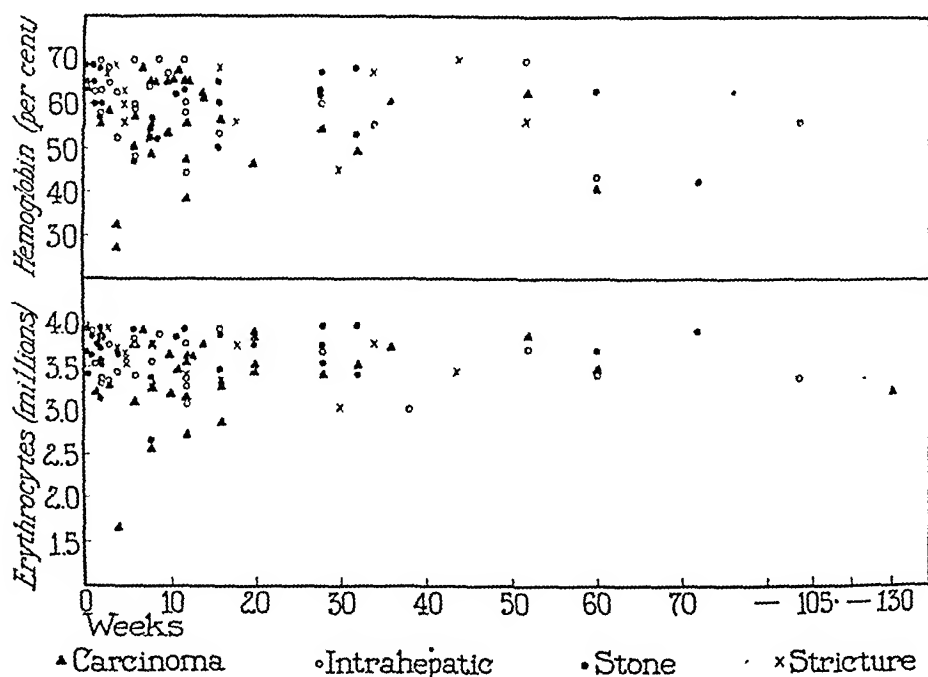


FIG. 1.—Correlation between the duration of jaundice and the degree of anemia in cases with a percentage of hemoglobin between 70 (Dare) and an erythrocyte count below 4,000,000 per c.mm.

Cholelithiasis. In this group are included all cases of jaundice due to stone in the common duct or to cholecystitis with cholelithiasis. Fever occurs in the majority of cases during an acute attack of colic due to cholelithiasis. Since the attack is of short duration fever was usually absent when these patients came to the Clinic; therefore, jaundice was the chief presenting symptom. Consequently, included in this group are patients with jaundice of several days' or weeks' duration who did not have fever between acute attacks of colic. Of the total number of 347 cases of jaundice, 142 belonged to this group, in 30 of which anemia was present (tabulation). Anemia occurred in 26 of 138 cases (19 per cent) observed in 1926 and 1927. The lowest percentage of hemoglobin was 42, with an average of 61. The lowest erythrocyte count was 3,400,000 and the average count was 3,670,000. Again a definite correlation could not be seen between the intensity of the anemia and either the duration or the intensity of jaundice (Figs. 1 and 2).

Stricture of the Common Duct. Since fever is present at some time in the majority of the cases of jaundice that is due to stricture of

the common duct, it is difficult to be certain that, when anemia was present in the cases of this group, infection may not have been a contributing factor. Thirty-one cases of stricture of the common duct were found, however, in which there was no history of fever and in which neither fever nor leukocytosis was present during the period of observation; in 14 of these 31 cases anemia was present (tabulation). Anemia occurred in 11 of 28 cases (39.3 per cent) observed in 1926 and 1927. The lowest percentage of hemoglobin was 45, with an average of 59. The lowest erythrocyte count was 3,010,000, with an average of 3,620,000. There was no definite correlation between the intensity of the anemia and either the intensity or the duration of the jaundice (Figs. 1 and 2).

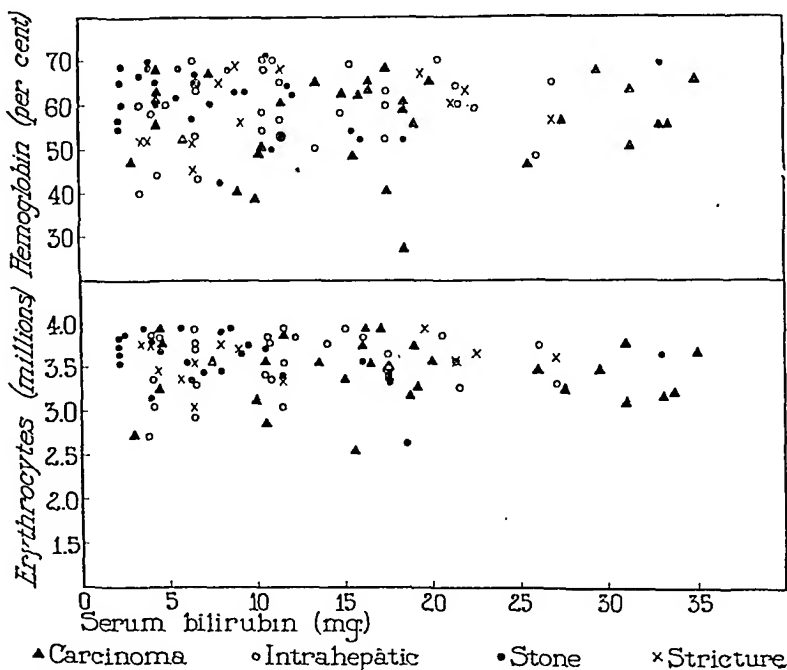


FIG. 2.—Correlation between the degree of jaundice and the degree of anemia in cases with a percentage of hemoglobin below 70 (Dare) and an erythrocyte count below 4,000,000 per c.mm.

Comment. The anemia that occurs in cases of obstructive and intrahepatic jaundice may be due to loss of blood, to increased destruction of blood, to decreased formation of blood or to a combination of these various factors.

It is well known that bile salts are hemolytic and the suggestion is commonly made that the anemia is due to the hemolytic action of these salts. There are many objections to this view. It is known that following a preliminary rise in the concentration of bile salts in the blood after obstruction of the common duct in dogs and human beings there is a gradual falling off in the level of these salts in the blood. We should expect, therefore, if bile salts were the cause of the anemia, to obtain anemia very soon after the onset of jaundice, when the concentration of bile salts is greatest. As

we have seen, this is by no means the case. In clinical cases, at least, the onset of the anemia is variable and may occur early or late. In dogs the anemia increases coincidentally with a fall in the concentration of bile salts in the blood.⁵ A point of great significance is that the concentration of bile salts necessary to produce hemolysis, as determined *in vitro*, does not occur in clinical or experimental cases of jaundice. Moreover, it must be remembered that there is increased resistance of the erythrocytes, and a protective action of normal serum against hemolytic agents.^{1,3,4} It is difficult to obtain direct experimental evidence on the question of hemolysis. The question is usually studied by determining the amount of bile excreted in dogs with biliary fistulas, but this is obviously out of the question in cases of obstructive or intrahepatic jaundice. It must be concluded, therefore, that the evidence in favor of increased destruction of erythrocytes in obstructive jaundice is relatively indirect and incomplete.

It was found more suitable to study experimentally the question of the formation of blood in dogs with ligated common ducts. Whipple and Robscheit-Robbins have shown that they could control the amount of regeneration of hemoglobin by variations in the diet. We have been able to adapt this method to a study of anemia in jaundiced animals and were enabled to study: (1) The effect of ligation of the common duct on regeneration of blood; (2) the effect of variations in the rate of regeneration on the degree of jaundice resulting from the obstruction. It was found that, in animals fed the basal diet, ligation of the common duct inhibits the regeneration of hemoglobin, whereas animals fed the diet containing liver are much more resistant to this effect of obstruction.² It was also found that the degree of jaundice, as measured by the serum bilirubin, varied with the degree of hematopoietic stimulation and the consequent activity of metabolism of pigment rather than on the total amount of circulating hemoglobin.

From the clinical standpoint, it is difficult to obtain quantitative data because of the many uncontrollable factors involved, such as the degree of obstruction or of hepatic injury, the degree and duration of jaundice and the character of the diet prior to admission of the patient to the hospital. The experimental results seem to show the importance of certain food factors in the prevention of anemia.

Experimentally, we have also shown that the degree of hematopoietic stimulation influences the degree of jaundice. If anemia develops in a jaundiced patient because of nutritional disturbance, we should, therefore, expect the degree of jaundice to diminish in intensity. Consequently, if anemia occurs in a jaundiced patient, independently of infection or of loss of blood, the amount of serum bilirubin diminishes so that the degree of jaundice alone does not give an accurate index of his condition. Under such circumstances, an anemic patient with low serum bilirubin may be a poorer risk

than one with a higher value of serum bilirubin in the absence of anemia.

Summary and Conclusions. Anemia frequently occurs in jaundice due to any cause, and it may be independent of infection or of loss of blood. Similar anemia occurs in dogs with obstruction of the common duct or with biliary fistula. In this series of patients there did not appear to be any correlation between the degree of anemia and either the duration or the intensity of jaundice, whether the jaundice was due to carcinoma, stone, stricture or intrahepatic disease. Anemia, represented by a value of hemoglobin below 70 per cent on the Dare scale, and below 4,000,000 erythrocytes occurred in 34 per cent of patients with jaundice due to carcinoma of the pancreas or biliary passages or to metastasis; in 31 per cent of patients with intrahepatic jaundice; in 19 per cent of patients with stone in the common duct or cholecystitis with cholelithiasis, and in 39 per cent of patients in whom jaundice was due to stricture of the common duct. Clinically, it is difficult to draw conclusions as to the cause of the anemia, since there are many uncontrollable factors, such as the reaction of each particular patient, the amount of obstruction or injury to the liver and the character of the diet before admission to the hospital. However, comparison is possible with animals in which anemia has been produced and studied. When this is done the conclusion is reached that the anemia is almost certainly not the result of the hemolytic action of bile salts and that nutritional factors are probably the most significant in its etiology.

Moderate or relatively severe secondary anemia may occur in cases of jaundice due to any cause, independently of infection or of loss of blood. Clinically, in this series of cases the intensity of the anemia was apparently independent of either the intensity or the duration of the jaundice. It is suggested that nutritional factors are of great significance in the etiology of the anemia occurring in jaundiced patients.

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NEPHROSIS.

A SURVEY OF THE LITERATURE, AND REPORT OF FOUR CASES.

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THERE are a number of affections of the kidney which are characterized by degenerative changes especially involving the tubules. These seem to be distinct from the inflammatory conditions which involve the glomeruli, and are also quite different from the arteriosclerotic diseases of the kidney. These affections have gradually acquired the name of "nephrosis." This term is not used in its etymologic sense, but, regardless of frequent objection, has retained such a widespread use that for the present, at least, we might as well accept it. The name was introduced first by Müller,¹ in 1905, and was intended to distinguish the degenerative from the inflammatory changes in the kidney. In 1914, in their monograph on Bright's disease, Volhard and Fahr² adopted this term as descriptive of degenerative affections of the kidney involving the tubules.

There are several different types of nephrosis. For instance, the kidney of pregnancy is generally placed in this class on account of albuminoid degeneration found in the convoluted tubules. This type is characterized clinically by albuminuria, edema, and possibly eclampsia during pregnancy. Amyloid nephrosis is another form. It occurs in the course of tuberculosis, especially of the bones, and is found in prolonged suppurative conditions such as osteomyelitis of nontuberculous origin. Here it is mainly characterized by albuminuria, and when edema is present it is generally combined with lipoid nephrosis. The kidney condition seen in mercuric poisoning also comes under the heading of nephrosis and presents a good example of the necrotic stage of this disease.

This disease, in which only tubular changes occur, is supposed to run a definite clinical course; without renal insufficiency, without hypertension, and without cardiac hypertrophy. Everyone understands, however, that kidney disease seldom pursues a clear-cut course and that one type of nephritis often merges into another. This may occur, obviously, in many variations and various degrees, and accounts for the many confusing differences we meet with in the study of kidney cases. One may say in general, that inflammatory processes affect the glomeruli, and the tubules become involved secondarily; while the degenerative processes affect primarily the tubules and the glomeruli secondarily. It is important to realize that confusion must always exist in diagnosing this disease, since in most cases one type of lesion becomes engrafted on the other.

For this same reason, nephrosis in its pure state is comparatively rare. Munk³ classifies the nephroses under the following types: (1) Albuminous degeneration; (2) fatty degeneration; (3) lipoid degeneration; (4) necrotic degeneration; (5) hyaline degeneration; (6) amyloid degeneration; (7) vacuolar degeneration; (8) glycogen degeneration (in diabetes).

We find, then, several different conditions giving rise to degeneration of the tubules, or what we have come to term nephrosis, for instance: (1) The kidney of pregnancy; (2) the amyloid kidney; (3) the bichlorid kidney. These are probably separated because of differences in etiology, and because there are some slight clinical distinctions; the common factor to all, however, is the tubular lesion.

That pure types of nephrosis occur, seems no longer a matter of dispute, and among the different types of this disease the one to receive the most discussion nowadays is the so-called "lipoid nephrosis." This is the same disease, characterized by the large white kidney, which used to be called chronic parenchymatous nephritis. It is what Volhard and Fahr² refer to as "genuine nephrosis" and what Epstein⁴ calls "chronic nephrosis." Pure cases of this disease have been reported by Volhard and Fahr² and later by Munk⁵ in their monographs, and it is to these authors that we owe most of our knowledge of this disease from abroad. In this country the interest in this condition has centered around Epstein⁶ following his introduction of high-protein feeding. Since then many cases of nephrosis have appeared in the literature. A good many of them seem to be cases of glomerulitis to which nephrosis has become an added factor and a good many seem to be cases of genuine nephrosis.

Lipoid nephrosis as an entity has definite characteristics which we find described by Munk.⁵ These features are: The insidious onset; its relative frequency in young people; the absence of etiologic factors; the pallor; the edema, which is generally cyclic in character; the albuminuria with few casts and no red blood cells; a low blood pressure; and an increase in the blood cholesterol. He also points out the apparently benign character of the disease. The urine is scanty as a rule, there may be lassitude, headaches and loss of appetite. Munk was the first to call attention to the doubly refracting lipoid bodies in the urine. To these factors Epstein⁶ adds: reduction in the total protein of the blood, stresses the "inversion of the normal ratio of serum albumen to serum globulin," and brings out the argument that nephrosis is of extrarenal origin, and apparently a metabolic disease accompanied by a lowered basal metabolism. Epstein⁷ records a case of nephrosis which finally developed into one of genuine myxedema. He also mentions three cases of nephrosis which developed during prolonged irradiation of the neck, involving the chest and thyroid.

The lowered basal metabolism certainly suggests that this is a metabolic disease. It appears so on the surface at least, until one is confronted with the fact that these basal metabolic readings are based on water-logged conditions. These individuals are edematous and this must affect the test considerably. The disturbance, however, is apparently not measurable in basal metabolic determinations since only 60 per cent of Epstein's cases show subnormal findings and these ranging only from -10 to -22 . On the other hand, he finds that these patients tolerate enormous doses of thyroid extract; doses of 15 to 60 grains of thyroid per day being necessary in some cases. This treatment must often be continued over long periods of time before a metabolic response is elicited. He finds that thyrotoxic symptoms do not result as long as there is an existing hypercholesterolemia, and suggests that the blood cholesterol be used as a measure of thyroid therapy in these cases. This seems to point to some profound metabolic disorder, and since it appears to be extrarenal, he has chosen the name "diabetes albuminuricus" to describe the disorder. In his opinion the extrarenal factors are of prime importance; the tubular degeneration is a consequence, and not a cause of the disease. Hence, he prefers that the term "nephrosis" shall take in all kidney conditions where the dominant lesion is tubular degeneration; but since lipoid nephrosis is not in a strict sense a kidney disease, he prefers the term diabetes albuminuricus. In diabetes the glycosuria is the result of a perversion in carbohydrate metabolism, so in this disease, the albuminuria which is the chief symptom, is the result of a perversion of the protein metabolism.

Munk's cases of lipoid nephrosis and Epstein's cases of chronic nephrosis seem to be identical and appear to be a definite disease entity despite the refusal of some authors to recognize it. It seems to me that we have cases enough now reported by reliable authors to convince the most skeptical. Beside Volhard and Fahr's, Munk's and Epstein's cases, there are numerous others listed in the literature, many of which appear to be true nephrosis and some of which seem to be mixed in type. Some authors complain that they are unable to find cases of a pure form and on account of this are inclined to disbelieve in its existence. The pure cases of nephrosis, however, are rare; the majority which we see are cases of glomerular nephritis with a superimposed nephrosis. These are generally the cases in which we find red blood cells in the urine. Munk's original conception was that the condition in the tubules is at no time the result of inflammation, and this I believe is the general opinion now. There are still some differences of opinion, however; Elwyn⁸ believes the albuminuria is the result of injury to the glomerular and capsular epithelium by a previous acute diffuse nephritis which has subsided. Murphy and Warfield report 4 cases. One of these cases was studied from beginning to end, and on examining the kidneys they found no evidence of any glomerular inflammatory condition; the

disease was purely tubular. Another point these authors bring out is the tendency to exacerbations and remissions; that is, the cyclic character of the edema which they claim is the rule. Mason¹⁰ reports a case of what seems to be pure nephrosis which he followed for thirty months, and which finally died of miliary tuberculosis. The kidneys showed a typical contracted nephrotic kidney without signs of inflammation. Kaufman and Mason¹¹ reported 3 cases (deaths from infection) which they believe typify the life history of nephrosis. Their first case showed all the clinical requirements of an early nephrosis, and at autopsy showed a large white kidney; the glomeruli were normal, but the tubules were dilated and filled with a pale-staining structureless material. Some of the tubular epithelium had desquamated, while the rest was granular and hazy in outline. There was no inflammatory exudate, and no increase of fibrous connective tissue. The second case, in addition to the characteristics of Case I, showed a moderate rise in blood pressure and some impairment in the nitrogen excretion. The kidneys were contracted. The third case showed in the early part of his illness all the characteristics of Case I and in the terminal part showed the characteristics of Case II. At autopsy, this case showed secondary contracted kidneys. They believe that the true nephrotic kidney progresses into a secondary contracted one, as a result of an organizing process of degenerated cells, and not of cells primarily inflamed. Davidson¹² reports a case with autopsy with typical clinical findings. Microscopic examination showed that the glomeruli were singularly free from damage and that the typical tubular changes were present. Peters¹³ reports 6 cases, but only 1 of these seems to me to be a case of true nephrosis. Major and Helwig¹⁴ report a case fulfilling the clinical requirements, but the glomeruli showed a mild glomerulitis. Rabinowitch and Childs¹⁵ cite a case, but their patient had hypertension, and was probably a chronic nephritic with a superimposed nephrosis. Rigler and Rypins¹⁶ report 3 cases which conform clinically to Epstein's nephrosis; one was a child, and a post-mortem examination showed the large white kidney. McElroy¹⁷ reports 2 cases in negroes; the first case was preceded by tonsillitis, and by the presence of occasional red blood cells in the urine. This might be considered a mixture of acute nephritis and nephrosis. The pathology of the kidney, however, in this case was that of nephrosis so that occasional red blood cells in the urine are permissible just as they may be found present quite normally in health. There was no sign of inflammation in the kidneys. The second case was complicated by syphilis. Munk⁵ gives syphilis as a cause of this disease. Cases of nephrosis in children occur frequently. Twenty-three of these have been reported by Clausen,¹⁸ 26 by Davison and Salinger,¹⁹ and 13 by Boyd.²⁰ Christian²¹ states that in some twenty odd years of interest in the subject, he has seen no such cases. All his cases, apparently having all the criteria as outlined, have shown

quite marked glomerular lesions. There is not much doubt in the minds of those who have studied this subject, however, that nephrosis does occur and occurs as a pure tubular degeneration with definite and characteristic findings.

Diagnosis. The characteristics then of nephrosis are: (1) A gradual onset and a protracted course; (2) edema, anasarca, and effusion in the serous cavities; (3) oliguria, and a high specific gravity; (4) marked albuminuria and occasional cylindruria; (5) the absence of increased blood pressure; (6) the absence of nitrogen retention in the blood; (7) marked increase in the cholesterol content of the blood; (8) reduction in the total protein of the blood serum; (9) inversion of the normal ratio of albumin to globulin; (10) the presence of doubly refracting lipid bodies in the urine; (11) it tends to occur more commonly in younger individuals; (12) there seems to be some relationship to states of hypothyroidism.

The edema and albuminuria are the most marked features. These features have been pointed out by Murphy and Warfield⁵ as particularly cyclic in character. Epstein⁶ explains the edema on the basis of a disturbance in the balance of the osmotic pressure between the tissues and the blood.

It is rather interesting that these patients as a rule show a lowered resistance to disease. Most of the deaths occur from pneumonia, empyema or peritonitis.

Pathology. The kidneys in these individuals are large and later become contracted. The capsule strips easily. There are no hemorrhages to be made out, and no signs of inflammation. McElroy¹⁷ finds the cortex widened. The normal markings are obscured and opaque spots corresponding to the deposition of lipoids may sometimes be seen. Microscopically the glomeruli may show focal degenerative changes characterized by widening, and swelling of the capillary walls and of the parietal layer of the capsule; double refracting substances are seen in old cases, and here and there is seen slight nuclear increase. The proximal convoluted tubules are chiefly involved, showing fatty degeneration of the epithelium, or lipid infiltration. Sometimes there is desquamation of the degenerated cells, exudation of albumin into the lumen, widening of the tubules with flattening of the epithelium, casts and efforts towards regeneration.

Etiology. The etiology of nephrosis is obscure, but several theories have been offered. The general impression prevails that it is a disease of extrarenal origin. In 1916, De Renzende²² reported spontaneous cure of a case following influenzal pneumonia. He also quotes a case reported by Allbutt very similar to his. He seems to think that the cure was due to some foreign protein reaction. Marriott,²³ in 1924, reported the recovery of a case following treatment of the nasal sinuses. Clausen¹⁸ believes the disease to be due to a toxic substance, and finds it associated

with staphylococcus infection principally of the nasal sinuses, and believes it to be a general disorder due to focal infection. In 11 cases, he finds nasal sinus infection invariably present. Aldrich²⁴ reports 7 cases; all had definite nasal sinus infection and successful drainage gave constant and prompt relief. Many attacks of nephrosis subsided with the spontaneous improvement of nasal sinus infections. Tonsillectomy was done in all his cases but no beneficial effects on the nephrosis were noted. Epstein's²⁵ theory that it is a metabolic disease and entirely extrarenal is a popular one, especially in the face of the results obtained by thyroid feeding and high-protein diet. Elwyn⁸ feels that although nephrosis occurs alone, a glomerular nephritis is so commonly mixed with it that glomerulitis must not be overlooked as a cause. He believes a great many cases begin as an acute glomerulitis.

Treatment. The principal treatment of nephrosis consists in the removal of foci of infection with special attention to the nasal sinuses and with restoration of the lost body protein by high-protein diet. Also fluid restriction and salt restriction is advised. Epstein²⁵ has advocated feeding large quantities of thyroid extract and using the blood cholesterol as a control (enough extract must be used to effect a reduction in cholesterol.) He also takes care of the edema by replacing the lost blood protein by feeding a diet high in protein, free of fat and carbohydrate poor.

Prognosis. Regarding the prognosis, several authors report cures by the removal of foci of infection followed by high-protein feeding. Epstein²⁵ states "certain cases of chronic nephrosis are susceptible to complete cure by the intelligent and persistent use high-protein feeding and thyroid therapy." Intercurrent infections carry off most of these patients.

Case Reports. CASE I.—(16236R) female, single, born and lives in Pennsylvania. Employed as a stenographer and is aged forty-eight years.

On admission, April 24, 1925, patient complained of swollen legs and ankles, and had been told by her doctor that she had acute Bright's disease. She did not notice anything particularly wrong until January, 1925, when she first noticed that her urine was becoming very frothy. She went to her physician who informed her that there was a good deal of albumin in the urine. Her face and ankles became swollen, so that she was put on a diet at home. The urine was very scanty. She has suffered no pain or discomfort. There has been no dyspnea, in fact, excepting for feeling a trifle tired, the patient feels well. The only abnormal findings on physical examination were badly swollen feet and legs. The heart appeared to be normal. The urine contained granular and hyaline casts. There were no red blood cells. There was 0.2 per cent or more of albumin present in all specimens. It looked like an extremely bad nephritic urine, but on examining her blood we found her blood chemistry to be normal, or even below normal. Urea nitrogen was 9.45 mg. per 100 cc.; uric acid 3.6, and creatinin 1.2. The phthalein test showed a kidney function of 78 per cent for the two hours and when checked up later showed 51 per cent. The ratio between the day and night volume was normal. The specific gravity varied from 1.007 to 1.018, the patient, however, was drinking large quantities of water

at this time. From the clinical appearance and judging from the urine analysis, therefore, this case might easily be pronounced a severe nephritic, yet her other kidney studies and blood chemistry findings argues against nephritis. It occurred to us that we were dealing with a case of chronic nephrosis. In keeping with this diagnosis we next found that the plasma cholesterol was increased to 0.406 per cent. The basal metabolism was -20. The patient was somewhat anemic. The relation between the serum albumin and globulin was only done once, but was found to be normal. Her blood pressure was 120 systolic and 76 diastolic.

The patient was put on a high-protein diet, 150 gm., and thyroid extract 0.5 grain t.i.d. At the end of four days the edema had almost disappeared. The high-protein diet was then discontinued for fear of injury to the kidneys and the dose of thyroid extract was doubled. The swelling immediately reappeared and by the end of four days was again as bad as ever. It was then decided advisable to try the diuretic effect of calcium chlorid, 12 gm. per day, on the patient. The result was an immediate diuresis and decrease in the edema, so that the patient lost 6½ pounds in weight in the following three days. The patient was discharged and ordered to continue this treatment. A letter from her one month later, reported that she was feeling "just fine" and the edema had not returned.

On returning home this patient continued to use thyroid extract, 0.5 grain t.i.d. and calcium chlorid, 4 gm. t.i.d. She wrote me on October 24 complaining of indigestion and urticaria in the form of hives. We then changed her medicine to calcium lactate and parathyroid, 0.05 grain t.i.d. She immediately improved and in a letter from her dated April 25, 1929, she states that she has never had any swelling of any kind since. She feels well in every way and apparently has nothing at all the matter with her.

Case Summary. This case seems to have been one of genuine nephrosis. The disease has entirely cleared up and after four years has shown no sign of return. Treatment consisted of the extraction of abscessed teeth, high-protein diet, thyroid extract, large doses of calcium chlorid, and finally giving her parathyroid and calcium lactate. Just which of these therapeutic measures resulted in the cure is difficult to say. The high-protein diet appeared to be the principal factor at first, but on discontinuing this, the calcium chlorid seemed to have the same effect. In any event, this patient finally recovered after the high-protein diet had been discontinued. The thyroid extract was given with all the other medications, so that it would seem that this and the calcium chlorid was the principal factor.

CASE II.—(26950R) female, married, aged forty-one years. Employed as a practical nurse.

The patient was admitted in November, 1928, complaining of kidney trouble. Her history was to the effect that six weeks prior to admission her legs began to bloat for the first time. They improved a little and then she had a relapse. The edema increased so that she was suspected of having nephritis and the urine consequently examined by her home physician. It was found to boil solid, and on consultation with one of the members of our staff, nephrosis was suggested. The patient was then brought here for study. There were no symptoms of any kind except the swelling of the legs. She had never had any previous kidney upset and had had her urine examined twice a year for some time, always finding it normal. In the past the only diseases from which she suffered were measles, whooping cough and chicken pox. She had had one child, who is aged twenty-one years. The family history was negative.

Physical examination on admission showed very marked edema of the legs with some general anasarca. She weighed 215 pounds. Her blood pressure was 108 systolic and 90 diastolic. The tonsils were diseased. The

teeth had been entirely removed. The remainder of her examination was negative.

Laboratory reports showed that the urine coagulated solid. There were no red blood cells present. Specimens contained some finely granular and coarsely granular and hyaline casts. The phthalein test showed a kidney function of 37 per cent for the two hours. Blood count on November 15 showed erythrocytes, 5,500,000; leukocytes, 10,000; hemoglobin, 93 per cent; the differential count was normal. The specific gravity of the urine varied from 1.011 to 1.030 but on nearly all occasions showed a high specific gravity. Culture of the urine was negative. The blood Wassermann was negative. Blood chemistry studies on November 15, 1928, showed blood sugar, 0.075 per cent; urea nitrogen, 10.9; uric acid, 5.2; creatinin, 1.4; calcium, 9.3 mg. per 100 cc.; cholesterol, 0.44 per cent. A basal metabolism on November 17 was -21. On November 19, the non-protein nitrogen (serum) was 18.4 and total nonprotein nitrogen (plasma) 16.7 mg. per 100 cc.; total protein serum, 3.37 per cent; total protein plasma, 3.66 per cent; serum albumin, 1.89 per cent; plasma albumin, 1.66 per cent; serum globulin, 1.48 per cent; plasma globulin, 2 per cent. On December 12, urea nitrogen 12 mg. per 100 cc. On December 14, basal metabolism -39. January 8 blood calcium, 8.8; urea nitrogen, 11.2; creatinin, 1.6 mg.; cholesterol, 0.557 per cent; March 1, 1929, basal metabolism -10; blood sugar, 0.094; urea nitrogen, 16.3; cholesterol, 0.292 (this was following several months of thyroid extract and high-protein diet treatment).

This patient was here under observation for five months. At first diuretics were tried, but to no avail, so that a week or two after her admission she was put on a high-protein diet. This consisted of protein, 120; fat, 50; carbohydrate, 120. Also she was given 5 grains of thyroid extract per day. She began to lose weight and the edema began to disappear, so that one month later her weight was 169 pounds, showing a loss of 40 pounds. Her blood pressure remained low and she developed no anemia during her stay. The thyroid extract then was reduced to 1 grain daily. The patient immediately began to develop edema and gained weight again. During the whole time she was here the proteins were kept up to a level of about 120 gm. During the period in which the thyroid extract was cut down to 1 grain per day, I gave her parathyroid (Collip's) for one week, during which time the patient gained a pound per day. The week following this, on discontinuing the parathyroid, she was tried on calcium chlorid, 12 gm. per day. She gained a pound per day also on this treatment. The thyroid extract was then raised to 3 grains per day, during which time she continued to gain weight slowly until she reached 196 pounds again. Then for some unknown reason, and without changing the medication or treatment, she began to improve. The edema decreased and she was finally discharged, weighing 160 pounds. Her diet at discharge was protein, 120 gm.; fat, 50; carbohydrate, 120. Medication—thyroid substance 3 grains daily.

Case Summary. This case also answers to all the requirements of nephrosis. Unfortunately we have no apparatus at present for the detection of the double refractile bodies, so that they are not given in any of these cases. This patient improved on the thyroid extract and high protein. She seemed to grow worse on parathyroid (Collip) and calcium chlorid. The cyclic character of the disease was apparent, however, in this case. She showed relapses and remissions when the medication was not changed. The final improvement was marked and we expect to follow this case to its conclusion.

CASE III.—(26555R) a female, aged thirty-nine years, occupation, clerk in a bank. Was admitted September 24, 1928. Complaint, kidney trouble.

She described a general bloating of the body which began in the feet about two months prior to admission here. She speaks of being unusually tired since last spring. She was examined for insurance six months prior to coming here and pronounced well except for diseased tonsils, was passed for insurance also a year ago. Thinks her whole sickness dates from a severe cold beginning about July 4, 1928. She had been accustomed to have a great many colds in the head. Past illnesses—measles, mumps, scarlet fever in childhood. Married three years, no pregnancy. Patient worked very hard in the bank in the day time and took correspondence courses at night. Family history negative.

Physical examination on admission showed her blood pressure 118 systolic and 70 diastolic, considerable puffiness around the eyes and face and marked edema of the legs and ankles. Tonsils diseased. There was a slight thyroid adenoma. Remainder of the examination negative.

Fluoroscopic chest examination was normal. Dentograms were normal. Blood count showed erythrocytes, 4,700,000; leukocytes, 11,200; hemoglobin, 80 per cent; neutrophils, 81.4 per cent; lymphocytes, 17.3 per cent; eosinophils, 1 per cent; basophils, 0.3 per cent (patient had a severe cold at this time). Urinalysis showed albumin ++; occasionally finely granular and hyaline casts, many erythrocytes and many leukocytes. The phthalein test showed 66 per cent for the two hours. The specific gravity of the urine varied from 1.007 to 1.023. Blood sugar was 0.082 per cent; urea nitrogen, 10.8 mg. per 100 cc. Blood cholesterol, 0.596 per cent; total serum protein, 4.92 per cent; serum albumin, 2.36 per cent; serum globulin, 2.56 per cent; total nonprotein nitrogen 23.6 mg. per 100 cc. Blood Wassermann was negative.

At first the patient was thought to be an acute nephritic and placed on a special diet low in protein. She seemed to improve a little but this was probably due to the fact that she was kept in bed. The edema, however, only improved slightly. On October 8, the tonsils were removed. At this time the important factors in the case were marked edema and marked albuminuria with no increase in blood pressure and no retention of nitrogen in the blood. She also had an oliguria and the specific gravity of the urine was high. There were, however, erythrocytes and casts in each specimen, which seemed to complicate matters, but on finding the high-blood cholesterol and the reversed ratio of globulin, we decided that this was a case of nephrosis.

She was very sick after tonsillectomy and the edema grew worse. On October 14, we gave her 100 gm. of protein per day but on account of her poor appetite she could not eat all of this. This patient left on October 27, about a month after coming here, and was little, if any, improved from her condition when she entered. No thyroid extract was given to this patient.

Several letters from her since report no improvement. I do not believe she keeps up the high-protein diet and have advised her physician to carry on with large doses of thyroid extract and also with the high-protein diet.

Case Summary. I believe this case to be a mixture of nephritis and nephrosis. There were casts and red blood cells in all specimens of urine. The onset was rather sudden following an acute cold. On the other hand, the blood pressure was low, there was no nitrogen retention in the blood, and the kidney function tests were good. Also the blood cholesterol was very high and there was an inversion of the albumin globulin ratio. She reports no improvement, but she discontinued her high protein at home and to date has been given no thyroid extract.

CASE IV.—(12607) a male, aged forty-five years, occupation, bookkeeper. Admitted October 15, 1923. Complaint swelling of the legs, shortness of breath, weakness.

This patient had not been well since an attack of influenza in 1920. In the spring of 1923, he noticed his ankles were swelling and in July, 1923, was obliged to give up work because of weakness and shortness of breath. The family history was negative. The patient was married and had one boy and one girl, both healthy. His habits had been normal. His past illnesses included measles and scarlet fever thirty years ago. In 1920, he had severe influenza. The edema had been very marked since the previous May.

On physical examination the patient was bedridden, had marked edema of the legs, his blood pressure was 158 systolic and 110 diastolic. The edema extended up over the back and abdomen. The heart was regular with no murmurs. There was free fluid in the abdomen.

The urine coagulated thick. There were innumerable hyaline, waxy, and finely granular casts. There were occasional erythrocytes and many leukocytes. The phthalein was 41 per cent for the two hours. The specific gravity of the urine varied from 1.030 to 1.045. The same urine picture obtained in all specimens except for the absence of red blood cells in most specimens. The blood Wassermann was negative. The blood count showed erythrocytes, 4,220,000; leukocytes, 8,400; hemoglobin, 90 per cent; neutrophils, 48 per cent; lymphocytes, 48 per cent; transitionals, 1.6 per cent; eosinophils, 1.6 per cent; basophils, 0.8 per cent. Blood sugar, 0.125 per cent; phosphates, 4.85 mg. per 100 cc.; calcium, 9.1, uric acid, 3.8; urea nitrogen, 21; creatinin, 1.2 mg. per 100 cc.; plasma bicarbonate, 52 volume per cent.

This patient had been on a salt-free, low-protein diet but on October 24 he was put on one high in protein. When he left for home two weeks later there was no improvement.

Patient returned in October, 1924. During the intermission he had continued on a full protein diet with gradual improvement so that by January 1, 1924, he was out of bed and by April he was able to go fishing and boating. By July, he was back at work again without any distress of any kind. On admission in October his blood pressure was 146 systolic and 84 diastolic. The edema had disappeared with the exception of some slight pitting along the shin bones. The urine still coagulated solid, however, and still showed granular, waxy and hyaline casts. The kidney studies showed marked deterioration. The phthalein was only 6 per cent for the two hours. Blood sugar was 160; plasma Co_2 , 40 volume per cent; urea nitrogen, 35; uric acid, 5.8; creatinin, 2.1 mg. per 100 cc.; cholesterol, 0.319 per cent.

It was decided that there was a decided mixture of nephritis in this case and that the high protein was irritating the kidneys so that he was allowed to go home and cut down on the protein. He returned again in May, 1925. In the meantime, he had been eating a balanced diet and stated that he had been gradually improving. He had been working every day and felt fine until about two weeks prior to returning, when he complained of feeling "dopy." At this time his blood count showed erythrocytes, 3,470,000; leukocytes, 11,200; hemoglobin, 61 per cent; neutrophils, 71.3 per cent; lymphocytes, 23.7 per cent; large monos, 2.3 per cent; eosinophils, 2.6 per cent; basophils, 0.2 per cent. The urine still showed the same picture, coagulating solid. There were red blood cells present with casts. Urea nitrogen was 23.8 mg. per 100 cc., the blood cholesterol was 0.319 per cent. Ten days later, while at home, this patient had a convulsion and died in a few minutes.

At autopsy, the kidneys measured about 8 by 4 by 3 cm. The capsules stripped with difficulty. The surface was very granular and reddish gray in color. On section, the cortex in some places was not more than 1 mm. in width, and not more than 3 mm. at points of greatest width. The

striations were entirely lost. Microscopically, they showed marked increase in fibrous connective tissue throughout the entire cortex. In many areas there was diffuse cellular infiltration and occasional clumps of lymphocytes. The tubules for the most part were dilated and lined by low cuboidal epithelium. In some places there was granular debris filling the tubules and in other places a castlike substance. The glomeruli were replaced by fibrous connective tissue.

Case Summary. This case appears to be a mixture of nephritis and nephrosis. At first the nephrosis seemed to predominate and to improve on high-protein diet, so that from a bedridden condition he was able to return to work. He developed a renal insufficiency ultimately and died as a result.

Conclusions. Pure cases of lipoid nephrosis are rare. They constitute a real and definite entity, however, and are amenable to treatment. We have here reported 2 cases of "genuine nephrosis" and 2 mixed cases, one of which came to autopsy. Of the 2 "true" cases, one is cured and one improved on treatment.

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SIX FATAL CASES OF DIABETIC ACIDOSIS.

WITH SPECIAL REFERENCE TO THE OCCURRENCE OF ACUTE
PANCREATIC NECROSIS IN ONE AND SEVERE
NEPHROSIS IN ANOTHER.

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NINE cases of diabetic coma were studied at the Cook County Hospital this year, with the particular purpose of investigating a series of diabetic acidoses of the type which is fatal in spite of treatment according to an accepted program. All of them, although complicated, fell properly into the class of diabetic acidoses when measured by a combination of the usual clinical and laboratory criteria. All were poor risks at the start; 4 recovered and 5 died.

The benign cases are not detailed since their recovery was in no wise remarkable. The complications may be noted: One was complicated by an extensive and acute membranous sore throat, not diphtheritic; a second by a subacute purulent otitis media and chronic malaria; a third by a huge carbuncle of the neck. The fourth case was complicated by a latent thyrotoxicosis, and entered again later to become one of our "fatal" group (Case I). It may be further noted that despite such handicaps, these patients gave prompt clinical and chemical evidence of good response to treatment.

The fatal cases are here presented, together with one other similar case not in the series, but included because of its unusual kidney lesions. They represent a group of fatal diabetic acidoses in which clinical data combine with necropsy findings on 5 of the 6 cases to throw light on their failure to recover under treatment.

All cases were handled on a similar régime. Insulin was given every six hours. Glucose was administered as milk, orange juice or sugar and water, by mouth, or subcutaneously in 5 per cent solution, or intravenously in 50 per cent solution. Alkalies were given in 4 instances. Fluids, gastric lavage, external heat, enemata and stimulants completed the therapeutic armamentarium. Dosage is indicated on Charts I and II. Blood chemistry determinations were made at the beginning of each period.

Intravenous alkali, when used, was given in 5 per cent solution, 15 gm. of sodium bicarbonate and 0.3 gm. of potassium bicarbonate being dissolved in 300 cc. warm double distilled sterile water immediately before infusion. After a few cubic centimeters of clear water this was followed by 5 cc. of 5 per cent calcium chlorid. This combination of salts was suggested by Dr. R. W. Keeton, of the

College of Medicine of the University of Illinois, as being one which would approach a replenishment of depleted alkali in something like physiologic proportions. The injections were made by a gravity apparatus and were prolonged over forty-five to sixty minutes.

Blood sugar was determined by the Folin-Wu method, blood plasma carbon dioxid combining power by the Van Slyke method, urine sugar by Haynes and Benedict's methods and acetone bodies by the nitroprussid and ferric chlorid tests.

For anatomic descriptions and their interpretation I am indebted to Dr. R. H. Jaffé, pathologist of Cook County Hospital.

Case Summaries. CASE I.—*Diabetes and Thyrotoxicosis.* A white woman, aged thirty-two years, suffering with diabetes and thyrotoxicosis, entered the hospital six times.

On her *first admission*, October 3, 1927, she complained of weakness, nervousness, excessive perspiration, palpitation, polyphagia, weight loss from 185 to 110 pounds and exophthalmos which had been present one year, starting with an obscure febrile illness of three months' duration. *Examination* at this time revealed a thin, pale woman with normal temperature; pulse, 120; respiration, 36; blood pressure, 130 systolic and 85 diastolic. Exophthalmos, cardiac hypertrophy, a systolic murmur at the apex and an enlargement of the thyroid were noted. There was glycosuria but no acetonuria. The basal metabolic rate was +35. The thyrotoxicosis was not treated; the glycosuria was controlled without insulin on a diet of carbohydrate, 65; protein, 65; fat, 100.

Subsequent to this, and prior to her final entry, the patient went into typical diabetic coma five times; four times she was treated at Cook County Hospital, and the essential data of these admissions is summarized in Chart I. The respective dates of these entries were: February 2, 1928; October 10, 1928; January 11, 1929; March 11, 1929. During the entire period she evaded any careful management. The prodromal symptoms of her coma were each time the usual headache, stupor and vomiting, varying irregularly from one to seven days in duration, and each time she recovered promptly, only to leave the hospital before diet and insulin could be properly adjusted. Further readings of the basal metabolic rate were +92 in February, and +82 in March, 1928, but surgical treatment of the condition was not urged and Roentgen ray treatment was refused.

Her *final admission* was on May 19, 1929. She had been feeling fairly well up to twelve hours before entry, when she complained only of headache; a few hours later she was discovered in coma. On *examination* the temperature was 97° F.; pulse, 80, and almost imperceptible; respirations, 20; blood pressure, 70 systolic and 40 diastolic; weight, 50 kilos (estimated). She was irrational, able to swallow, but not to answer questions, and her respirations were sighing and groaning, but not so deep or frequent as is typical of diabetic coma. There was an acetone odor to the breath, the skin was dry and the face pink, exophthalmos and the goiter were still present. Scattered crackles were heard at the right lung base, and there was a palpable friction rub over the anterior right chest. Glycosuria, acetonuria, hyperglycemia and a lowered blood carbon dioxid confirmed the *diagnosis* of diabetic coma. *Treatment* was instituted and is summarized on Chart I. She appeared to rouse from her stupor at the beginning, but soon the signs of a pneumonia developed at the right base; the patient sank into a toxic state, and in spite of all therapy she died the next morning.

Necropsy. The chief findings were atrophy of the pancreas, hypostatic confluent bronchopneumonia of both lower lobes and a nodose colloid

goiter with central fibrosis. The pancreas was moderately firm with fairly distinct lobulations. Microscopically there was a marked increase in the interlobular fat tissue, and many fat cells invaded the lobules. There was a metaplasia of the epithelium of some of the larger ducts. Small areas of atrophy of the acini occurred in the center of the lobules. The islands were scanty, and although those present were all preserved, they were occasionally rather small. Additional findings were fibrous obliteration of the right pleural cavity, cloudy swelling of the myocardium, fatty changes and parenchymatous degeneration of the liver; acute inflammatory reaction of the spleen with anemic infarct, slight atheromatosis of the aorta, decreased lipid content of the adrenal cortices, multiple follicular cysts of the ovaries and chronic erosive cervicitis with multiple subepithelial abscesses and cysts.

CASE II.—*Diabetic Coma, Pulmonary Tuberculosis and Unexplained Convulsions.* A white man, aged forty years, entered the hospital in deep coma. The only history available was that he had had diabetes for one year, that he had been up and about until the night before, and that a physician noted both glycosuria and convulsions several hours before entry. On examination the temperature was 97° F.; pulse, 120; respirations, 26; blood pressure, 98 systolic and 78 diastolic; weight, 50 kilos (estimated). The patient was small, lightly built, emaciated, dehydrated and in complete coma. Generalized clonic convulsions occurred every fifteen minutes, lasting one to two minutes, and eventuated in periods of apnea of about thirty seconds. The skin was dry and scaling, there was an acetone odor to the breath, and the breathing was very weak and shallow. There was neither choked disk, retinitis nor any evidence of middle-ear infection to suggest an explanation of the convulsions. Reflexes were absent. Urine showed sugar, acetone, albumin and casts. The spinal fluid was normal. *Diagnosis* was somewhat doubtful: Severe diabetic acidosis seemed certain and was confirmed by the blood chemistry reports (Chart I), but uremia, cerebral accident and insulin shock were likewise considered as a possible basis of the convulsions. *Treatment* was started, but was ineffective; the convulsion continued and death ensued in four hours.

Necropsy confirmed the diagnosis of diabetes, but revealed some unsuspected lesions. The chief findings were atrophy of the pancreas, ulcerous pulmonary tuberculosis of the right upper lobe with a healed primary lesion of the left lung and bilateral obliterative pleural adhesions and fibrocaseous tuberculosis of the tracheobronchial lymph nodes; primary contracted kidneys with fatty changes and cloudy swelling; and purulent seminal vesiculitis. The pancreas was slightly softer than normal, with a moderate increase in the interlobular and intralobular connective tissue. There were small areas of atrophy of the parenchyma. The acinar cells contained much fat and the medium-sized arteries were infiltrated by lipid material. The islands of Langerhans could not be discerned. The brain was both macroscopically and microscopically normal. Additional findings were extensive atheromatosis of aorta and coronaries; eccentric hypertrophy of the heart with dilatation; brown atrophy and parenchymatous degeneration of the myocardium; mucopurulent tracheobronchitis; acute infectious splenic tumor; cloudy swelling, brown atrophy and fatty changes in the liver.

CASE III.—*Diabetic Coma and Ischiorectal Abscess.* A negress, aged forty-nine years, entered the hospital on May 6, 1929, in moderately good condition, complaining of pain in the rectal region of one week's duration, which for three days had been associated with constipation. For many months she had had a nocturia of about six times nightly. *Examination:*

Temperature, 102.6° F.; pulse, 118; respirations, 24; weight, 100 kilos. The patient was an obese, colored female, with no remarkable findings other than a left ischioirectal abscess, which was opened and drained some 10 cc. of pus. By evening she was very thirsty and an acetone odor was noted on the breath.

Status when seen by us at 10.30 p.m.: Temperature, 98.4° F.; pulse, 180; respirations, 36; blood pressure, 200 systolic and 100 diastolic. She was semistuporous, but could swallow and would answer questions; there was mild dehydration and acetone breath; respirations were weak and shallow. Glycosuria and acetonuria, hyperglycemia and a lowered blood alkali were present. The *diagnosis* appeared to be diabetic acidosis complicated by intoxication from the abscess and hypertension. The general condition did not at first seem alarming, but the response to *treatment* was poor. A little mental brightening and an improvement in the pulse ensued upon the administration of the alkali, but the respirations became constantly feebler and more rapid, the pulse became imperceptible, the skin become cold and moist and she died within seventeen hours from the beginning of intensive treatment, although laboratory reports indicated that the metabolic disturbance had been in large part corrected. Data is on Chart I.

Necropsy. The findings were those of a generalized sepsis, with a general softening of the internal organs, acute infections of the spleen, and a large abscess of the left gluteal region. The pancreas weighed 112 gm., and was soft; microscopic sections were not made. Additional findings were hypertrophy and degeneration of the myocardium, cloudy swelling of the kidneys, congestion, emphysema and edema of the lungs and nodose goiter.

CASE IV.—*Diabetic Coma and Gangrene.* A negress, aged forty-nine years, entered the hospital on May 4, 1929, complaining of pain and discoloration of the right foot which had been present for ten days following the "picking" of a corn. Glycosuria had been discovered two weeks before. On *examination*, she was not acutely ill; the dorsum and toes of the right foot were involved in a dry gangrene. The patient was treated by diet and heat to the foot, but sank gradually into stupor.

Status when seen by us on May 6: Temperature, 97.6° F.; pulse not perceptible; apex beat, 80; respirations, 20; blood pressure, 80 systolic and 60 diastolic; weight, 60 kilos (estimated). The general condition was obviously poor; the coma was complete, with no response to questions, inability to swallow and absent reflexes; there was moderate dehydration and the breath was foul. Moderate glycosuria and acetonuria were present, along with a marked hyperglycemia and a definitely lowered blood carbon dioxide. *Treatment* was completely ineffective, and the patient died the next day. The data is summarized on Chart I. Necropsy was not permitted.

CASE V.—*Diabetic Coma and Acute Pancreatic Necrosis.* A colored man, aged twenty-eight years, entered the hospital on March 25, 1929, in deep stupor. The *history* was obtained from the wife and told of an illness of two weeks' duration with indefinite onset; the chief complaints were abdominal discomfort, described as a full "drawing" pain in the left epigastrium which was constant but not acute; vomiting occurred almost daily, usually after food, with blood flecks noted once; anorexia alternated with polyphagia; occasionally large meals were retained. Polyuria and polydipsia were noted for about one week. Constipation had existed for two days, but had been relieved by enemas. Previously the patient had always been healthy; he had used alcohol moderately. *Examination* on entry revealed a powerfully built, obese young negro, with temperature, 100.2° F.; pulse, 116; respirations, 56; blood pressure, 86 systolic and 50 diastolic; weight was estimated at 100 kilos. He was completely relaxed, unable to respond

CHART I. CASES I-II-III-IV

CHART I. CASES I-II-III-IV																	
CASE NUMBER	RESULT	NO. OF HRS. TO DEATH OR RECOVERY	URINE				BLOOD			TOTAL FROM BEGINNING TREATMENT TO RECOVERY OR DEATH.				REMARKS			
			Sugar	Acetone	Microscopic	Sugar	CO ₂ Vol. %	UREA N	Insulin UNITS	Glucose GMS.	FLUIDS	ALKALIES	OTHER THERAPY				
I Admission 2	RECOVERY	16	on Entrance	66%	++++	+++	375	24		180	70	700 cc. Orange juice 300 cc. Milk	8.0 gm. NaHCO ₃ oral Na Acetate oral K Citrate				
			on Recovery	0	Trace	0				21			caffeine 0.3 gm. q hr. x 6 3.5. enema gastric lavage				
	RECOVERY	7½	on Entrance	++++	++++	+++	300	24		125	39	240 cc. Water 390 cc. Orange juice	6.0 gm. NaHCO ₃ oral Na Acetate oral K Citrate				
			on Recovery	Trace	+	+	156	44									
	RECOVERY	16	on Entrance	++++	++++	++	600			170	175	250 cc. Milk	20.0 gm. NaHCO ₃ oral Na Acetate oral K Citrate	gastric lavage			
			on Recovery	+	Trace												
Admission 5	RECOVERY	14½	on Entrance	125%	++++	+++	556	22	98	20	1000 cc. Saline (Hypodermoclysis) 1200 cc. Water + Sugar 1400 cc. Milk			external heat 3.5. enema			
	RECOVERY		on Recovery	0.5%	+	0	315	50		99							
			on Entrance	125%	++++	+++	500	25	170	140	1600 cc. Saline (H) 1800 cc. Water 2400 cc. Milk	15.0 gm. NaHCO ₃ 0.3 gm. K HCO ₃ oral	external heat 3.5. enema adrenalin 10cc x 3 caffeine 0.3 gm. x 4 hyalin 20cc x 2	clinically out of coma for short time about 6 hours after entry			
	DEATH	31	on Recovery	Trace	+	0	566	24									
			on Entrance	+	++	Trace	628	26	16	50							
	II	DEATH	4	on Entrance	+	++	Trace	628	26	16	50						
III	DEATH	16½	Before death	2.5%	Trace	0	640	20									
			on Starting treatment	30%	++	+	500	32	160	68	3600 cc. Saline (H) 800 cc. Milk + Sugar 300 cc. Alkali (H) →	15.0 gm. NaHCO ₃ 0.5 gm. K HCO ₃ 0.25 gm. CaCl ₂	external heat caffeine 0.3 gm x 10 gastric lavage	vomited some of milk; last blood chemistry 10 hours before death			
	DEATH	15½	Before death	Trace	+	0	565	40	42								
			on Starting treatment	++++	+++	+	500	26	200	40	2400 cc. Saline (H) 400 cc. glucose and alkali (Intravenous) →	15.0 gm. NaHCO ₃ 0.5 gm. K HCO ₃ 0.25 gm. CaCl ₂	caffeine 0.3 gm. x 9				
	DEATH		Before death	++++	+++	+	500	28									

to questions or to swallow, with Kussmaul breathing, acetone breath and dry skin and mucosa. The lungs were clear. The abdominal wall was thick, firm and muscular, but relaxed and only moderately distended. No masses nor organs were felt and the percussion outlines were normal. Glycosuria and acetonuria were moderate; hyperglycemia and depletion of the blood alkali were marked; the white blood count was 12,500 and the blood and spinal fluid Wassermann reactions returned negative. The *diagnosis* of diabetic coma seemed probable, and when the temperature rose to 103° F. and vomiting persisted in spite of gastric lavage, a peritonitis was suspected. Although *treatment* was unsuccessful, there was a remarkable brightening following immediately upon the intravenous alkali, when the patient woke up, asked where he was and said he felt better. However, in ten minutes he lapsed back into stupor and died within ten hours from entry. The data are summarized on Chart II.

Necropsy. The essential findings were an acute necrosis of the pancreas with extensive fatty necrosis of the peritoneum. There were, in addition, a fatty infiltration of the liver, parenchymatous degeneration of the myocardium, infectious softening of the spleen, petechial hemorrhages of the gastric mucosa, hemorrhagic bronchopneumonia of both lower pulmonary lobes and slight eccentric hypertrophy of the heart.

The *pancreas* weighed 370 gm. and measured 20 by 6 by 3 cm. The capsule was covered by a thin fibrous membrane, and there were numerous necrotic areas on its surface, on the cut surface and in the surrounding fat tissue. Microscopy demonstrated these areas of necrosis to involve the parenchyma and the interstitial fat tissue. They were surrounded by zones of capillary hyperemia. There was swelling of the fibrocytes and loose accumulations of white blood cells. Outside of the necrotic areas there was a slight increase of the interstitial tissue. The islands were well preserved.

CASE VI.—*Diabetes, Pneumonia and Severe Nephrosis.* A white woman, aged thirty-seven years, a housewife, entered the hospital on October 17, 1928. She had been irrational for six hours. Previously, she had been for several weeks on a poorly controlled régime of diet and insulin for diabetes. *Examination* on entry showed a thin, pale woman with temperature, 98.2° F.; pulse, 118; respirations, 32; blood pressure, 122 systolic and 86 diastolic. She was confused, but could swallow and answer questions; respirations were deep and sighing. Glycosuria was marked, and acetonuria mild. A *diagnosis* of diabetic coma was made and she was treated as is detailed on Chart II.

The course was apparently puzzling. An original improvement was followed by a severe insulin reaction, and this by a confused mental state which persisted until she sank into coma again and died on the seventh day. Lung involvement was not suggested or suspected. Acetonuria disappeared promptly and did not return with the coma.

Necropsy. The chief findings were a chronic interstitial pancreatitis; a pneumonic process in the right lower and middle lobes with one small abscess; and a severe nephrosis. Additional findings were softening of the heart and spleen, sclerosis of the aorta and coronaries, bronchitis of the left lower lobe and decreased lipid in the adrenal cortices. Microscopically, the pancreas showed a diffuse increase of interstitial connective tissue and loose accumulations of leukocytes, lymphocytes and histiocytes. The islands were very scanty and those which were present were very small and composed of cells which were dark, nucleated and showed hyalin degeneration.

The kidneys were large, smooth and light yellow, with an irregular network of thin purple strands. The capsule stripped easily. On the cut

CHART II - CASES - I and II

CASE NUMBER	DATE and TIME	URINE			BLOOD		INSULIN GLUCOSE UNITS GRAMS	FLUIDS	ALKALIES	OTHER THERAPY	REMARKS
		AMOUNT	SUGAR	ACETONE	SUGAR	GLUCOSE					
I	3-25-28	500cc	100%	+++	600	16	15	2400cc saline (hypodermoclysis)		external heat	
	12:00 noon			+			35	200cc milk + sugar		gastric lavage coffain 0.3gm	gastric contents 300cc. brown fluid; Benzidine (+)
	2:00 PM						21	300 cc milk		S.S. enema	
	4:00 PM						50			coffain 0.3gm	milk given but all vomited.
	6:00 PM	complete fec.	+++	+++	500	18			150gm NaHCO ₃ 0.5gm KCl 0.25gm CaCl ₂	adrenalin 10cc	momentary brightening
	8:00 PM						40	200cc 20% glucose intravenous 300cc alkali			died; data immediately antemortem.
II	10:00 PM	complete 10cc	+	0	300	38	57.8		Natidol Naacetate K citrate	coffain 0.3gm x 4 gastric lavage	
	10-17-28 consec.		+++	+	ARB	28.9	100	water ad lib and with sugar throughout			
	10-18-28 6-hour		+++	0	318		80		same - 50 150gm		clinically improved
	10-18-28 periods: 12M-4AM etc.		+++	0	286		70	1600cc saline (H) 300 cc orange juice			emesis
	10-18-28 I		+++	0			50	200cc orange juice + sugar	same - 50 120gm		
	10-18-28 II		+	0	42		50	200cc orange juice + sugar			conscious
	10-18-28 III		0	0	28-300 PM		20	300 cc. orange juice + sugar		adrenalin 10cc.	insulin coma - 5:00 PM. recovered - 4:00 PM.
	10-18-28 IV						20				irrational
	10-19-28	*	+++	0			100	800cc. milk			conscious; complaining abdominal pain
	10-20-28		+++	0			120	1600cc. milk			very restless
	10-21-28		+++	0			100	1600cc milk			clinically seems quite well
	10-22-28		+++	0	425		275	400 cc. milk	same - 50 120gm		back in coma
	10-23-28		+++	0	460	72	60				died 8:00 PM.

surface the tissues were swollen and the pyramids poorly differentiated. Parallel to the border, in the cortex was a distinct whitish yellow line, 1 to 2 mm. thick. The outstanding microscopic features were a very marked edematous loosening of the stroma and a dilatation of the convoluted tubules. In the stroma the connective-tissue fibers were spread apart by a pale stained substance. The fibrocytes were swollen. There were occasional small perivascular accumulations of lymphocytes. The epithelium of the convoluted tubules was low cuboidal and in many of the cells were large and small vacuoles which did not take the fat stain. There was very little fat in the epithelium. The lumen was empty, or contained a foamy network of pale-stained granular material. The glomeruli showed a slight sclerosis of the tufts, but there was no swelling nor proliferation of the tuft cells. The afferent arterioles had a slightly thickened hyalin wall.

Discussion. In considering the group of cases as a whole, our first interest lay in discovering why they did not respond to treatment. Three reasons suggest themselves: (1) They might have been already overwhelmed by the process of acidosis when first seen; (2) they might have been suffering from a complication which so inhibited the power of insulin as to let the disease proceed as though untreated with this remedy (the familiar "insulin-resistant" diabetic); or (3) they might have been suffering from a complication itself fatal. Very roughly, and with overlapping, our 5 cases permit themselves to be considered as presenting three fairly distinct clinical pictures in which one or the other of these elements predominates.

Cases II and IV seem to fall properly into the first class. They were in a state of complete relaxation, unable to talk or swallow or understand, with abolition of reflexes, incontinence of urine and subsidence of Kussmaul respiration. This picture may be interpreted as a toxic exhaustion; patients once exhibiting it seem not to respond to any type of therapy. Whether this depression was due here to the acidosis rather than to the toxicity of the complicating process—ulcerative tuberculosis and gangrene respectively—is not certain. Neither showed the slightest response of any kind.

Case I comes under the second heading. Infection is an accident, which in any stage of diabetes, but especially in coma, is well known to interfere with the potency of insulin. Such interference is not always grave. However, it would appear that in Case I a pneumonic process, itself rather mild, nevertheless made it impossible to restore the patient to a normal metabolism and normal acid-base equilibrium. Examination of her records for testimony as to the inhibiting effect of the infection on insulin in her final entry discloses the following data: (1) Therapeutic régimes in all admissions were roughly similar. (2) On no other entry was there evidence of infection. (3) Symptoms of acidosis had not persisted longer in the final than in previous instances. (4) Laboratory findings infer metabolic derangements of about equal severity in all entries. Definite glycosuria and acetonuria were present each time;

blood chemistry readings are indicated on Chart I. (5) No obvious malignant factor appears in the final entry other than the infection. (6) Amount of insulin used to no benefit in the fatal entry was as great as that found to be effective four times previously. Data on Chart I.

One may reasonably conclude from all this that the mild early pneumonia, which was demonstrated at autopsy to exist at the time of the patient's death, caused a fatal outcome more through its inhibition of insulin than through its own toxicity.

It is interesting to note that the work of Lawrence⁹ suggests that the mechanism by which infection inhibits insulin may be through thyroid and adrenal stimulation. In this case we have clinical evidence of thyrotoxicosis from the time of her first entry. A basal rate in 1928 was +92 per cent. Although this overactivity of the thyroid was not apparently antagonistic to insulin in the previous entries in coma, it is possible that when the thyroid was further stimulated by the infection it was a significant factor in the fatal outcome. The question is also raised, whether the ease with which the patient developed severe acidosis may have been as much dependent on her doubly deranged metabolism as on her therapeutic negligence.

Finally, Cases III and V furnish examples of complicated diabetic coma, in which death seems rather to be due to the complicating factor than to the acidosis. The blood carbon dioxid levels were brought up to 40 and 38 respectively, the chemical and clinical signs of acidosis were relieved, and the patients died in a toxic state. Existence in Case V of an acute pancreatic necrosis will be further discussed; Case III, although showing locally only a large ischio-rectal abscess, gave postmortem evidence in the state of the other organs, of a generalized sepsis. The question of how far the diabetes aggravated the complicating pathology cannot be answered. Certainly acute pancreatitis often kills even without causing a marked upset of carbohydrate metabolism, and a large abscess may even in a normal person precipitate a fatal septicemia. Case VI, with its pneumonia and lung abscess, probably belongs with these.

Results of Alkali Administration. In turning to the results which followed on the use of alkalis in 4 of these cases, it is obvious that there was *a priori* not much to be expected from such medication. The original blood carbon dioxid reading, whatever its value in reflecting the state of acid-base equilibrium in the body, was above the fatal level in all instances: 32, 26, 25 and 16 volumes per cent. The patients were no doubt as ill from toxins as from depleted base, and the probable value of rapidly increasing the alkali reserve was at best questionable. One observation seemed to justify the attempt. There was in all these cases an acetonuria which was very slight in proportion to the degree of acidosis implied by the blood carbon dioxid findings. This suggested that these cases might have

an element of nonketone acidosis in them,^{1,13} and that alkali administration might be particularly indicated in their treatment.^{1,4,10,13} Unfortunately, neither our clinical results nor the chemical determinations admit of any conclusions about this point. It seems more likely, however, that the failure to excrete significant quantities of acetone bodies in the face of a low alkali reserve resulted in our particular cases from renal and vasomotor insufficiency, rather than from the existence in the blood and urine of unidentified organic acids. The finding of a small or decreasing urinary output in several cases (for instance Chart II) supports this more commonplace interpretation of the low acetone body output.

Our actual results were these: (1) In Case I 15 gm. of alkali by mouth made no change in the carbon dioxid level. (2) In Case IV 15 gm. of alkali intravenously had no greater effect. (3) In Case III, during the six-hour period in which 15 gm. of alkali were given intravenously, the carbon dioxid rose from 32 to 40. But the blood sugar dropped and glycosuria lessened in this same period so that there is evidence that insulin itself was active and might alone account for the slight rise. (4) In Case V, which coincidentally represented the most severe acidosis of the fatal group, during the first six hours the carbon dioxid rose only from 16 to 18 volumes per cent; during the second period, with similar insulin dosage but with intravenous alkali, the carbon dioxid was brought from 18 to 38 volumes per cent. In the same period continued hyperglycemia and glycosuria testify against activity of the insulin.

From this it will appear that there was only 1 case in which intravenous alkali seems to have effected a chemical improvement. The clinical benefit was very temporary. The 2 cases in which alkalies failed to alter the blood chemistry, whatever good one might have expected from such an alteration, may be taken to indicate either that enough alkali was not given, or that there existed a more subtle upset in acid-base balance than one which could be corrected by the simple gesture of pouring in bicarbonate.

Acidosis and Acute Pancreatic Necrosis. There occurred among these 6 cases at least 2 rather rare pathologic phenomena. Case V is one of acute pancreatic necrosis in the brief course of which a typical diabetic acidosis developed as a secondary but clinically dominant picture. This view of its pathogenesis is vouchsafed by the absence in the anamnesis of any diabetic symptoms antedating the acute illness, by the patient's state of overnutrition and fair hydration on entry, and by the necropsy findings. Although there is a fairly large number of cases recorded in which diabetes developed sooner or later after proven or inferred pancreatitis, or in which hyperglycemia gave evidence of deranged internal secretion during the period of acute necrosis, only 4 cases are comparable in developing an acute diabetic acidosis simultaneously with the pancreatic

syndrome. The first of these is reported by Caro and Winkler,² the second by Rodriguez¹¹ and 2 others are added by Warfield.¹⁴

In the 2 cases in which the point is mentioned, 1 reports complete destruction of the islands of Langerhans and 1 their destruction in the midportion and tail. In our own case, in spite of their apparently deranged function, the islands showed good anatomic preservation.

Nephrosis After Large Insulin Dosage. The postmortem finding in Case VI of the unusual nephrosis above described suggests a possible relationship between this kidney damage and the huge dosage of 1145 units administered during the six and a half days of treatment. Some degree of nephropathy accompanies almost every severe diabetic acidosis;³ albumin and casts were found on urinalyses in all these cases, and renal pathology was found in the 5 cases which came to postmortem examination. However, since the opening of the insulin era there has been evidence brought forth suggesting that insulin may at times play a rôle in producing a characteristic renal lesion. On the clinical side there are reports which possibly tend to show some correlation between the amount of insulin given and the degree of nitrogen retention which ensues.⁷ On the pathologic side are the reports of somewhat unusual types of renal changes of which our case is an example.

The typical "diabetic kidney" exhibits a nephrosis, characterized by a heavy fatty infiltration of the epithelial cells, and by a storage of glycogen in the epithelium of the loops of Henle in a zone macroscopically visible between cortex and medulla.⁵ In contrast to this, at least one observer, Kraus, reports a quite different picture found at section of 3 insulin-treated cases.⁸ They developed uremia immediately following their diabetic coma, dying ten, eight and five days after the beginning of treatment for the acute acidosis. (No abnormally large doses of insulin were given.) These kidneys were all greatly swollen, edematous and anemic, with a peculiar yellowish color which gave the macroscopic picture of fatty infiltration. Microscopically, however, there was no fat except that dependent on a lipemia in 1; instead there was a large collection of fluid in the convoluted tubules with a granular and hydropic degeneration of the epithelium and some swelling of the glomeruli. There was also the more usual glycogen zone. It will be seen that, although the author considered the picture a possible early nephritis instead of calling it a nephrosis, these kidneys answer to a description very similar to that of the kidneys in Case VI. Kraus does not himself consider insulin the cause of these changes, but thinks that the appearance of unusual kidney lesions in insulin-treated cases may perhaps be taken to mean that the prolongation of life which insulin makes possible, merely allows the damage due to acute acidosis to develop full blown. The massive insulin dosage in our own case, however, suggests that the hormone itself may in some

way be involved in the production of this renal picture in which the dominant elements are a marked edema involving the stroma, and a hydropic degeneration of the tubular epithelium—a picture similar to that described in chronic dysentery.⁶ Such a suggestion must, of course, be made all the more cautiously in so complicated a case, in which the patient suffered not only with diabetes, but with a pneumonic process in the lung.

That the patient was not kept out of coma in spite of the heroic insulin dosage is a fact worthy of comment. Study of Chart II and of the anatomic descriptions affords this probable explanation. The patient was presumably never, after the first few hours, suffering from a diabetic acidosis. The immediate and permanent disappearance of the acetonuria suggests this, as does the pallor which was noted on entry, and which is in sharp contrast to the flushed face of a patient typically affected with ketosis. Further, the continued albuminuria, the rising blood-urea nitrogen and the post-mortem findings of a nephrosis and a lung abscess indicate that there was sufficient disease in kidneys and lungs to account for her poor clinical condition. The terminal rise in blood sugar may well have resulted as much from the rather generous feeding of glucose, as from any ineffectiveness of insulin. The occurrence of a reaction forty-eight hours after entry testifies that insulin was active at least at the beginning of treatment.

For permission to report this case I am indebted to Dr. C. J. McMullen of the Medical Department of the University of Chicago.

Convulsions. Passing mention in Case II of the occurrence of convulsions may likewise be made. Convulsions in diabetic coma are a symptom infrequently observed. Blood chemistry in the case under discussion tends to rule out both insulin shock and true uremia as their cause. However, the finding of a primary contracted kidney on section reopens the possibility that the convulsions were a manifestation of a general arteriole spasm related to the kidney pathology, rather than a manifestation directly connected with the acidosis. That such an explanation of the convulsions is possible is suggested by Ricker in his discussions of arteriole spasm,¹² more particularly in relation to eclamptic convulsions. The brain was normal.

Summary. 1. Six cases of diabetic acidosis, fatal in spite of treatment, have been presented.

2. Clinically, or at autopsy, all these cases were shown to have been complicated by an infective or gangrenous process; 1 of them developed the diabetic syndrome secondary to an acute pancreatic necrosis; 1 of them, treated with huge insulin dosage, exhibited an unusual nephrosis.

3. Analysis of records suggests that death occurred either because treatment was instituted only after intoxication had already progressed too far, or because an infection inhibited the power of insulin, or because the complication was itself fatal.

4. Experiment with the use of 15 gm. of alkali in 4 cases showed significant change in alkali level in only 1 instance and permanent clinical benefit in none.

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SKIN HYPERSENSITIVITY TO PHENYLHYDRAZIN HYDROCHLORID.

REPORT OF A CASE.

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RECENTLY the subject of hypersensitivity has been stressed in medical literature, and it has been shown that the various tissues of the body may be susceptible to an almost innumerable list of

organic and inorganic substances. Some of these substances, such as the foreign proteins, are commonly recognized, as the cause of either localized or generalized evidences of hypersensitivity.

Others, such as the compound phenylhydrazin hydrochlorid, which not uncommonly causes untoward results when taken internally, must be indeed rare as a cause of reactions following skin contact, since a search of the literature has revealed only one previously reported case. Giffin and Conner¹ recently discussed the results following the internal use of this drug in the treatment of *polycythemia vera*, mentioning the progressive anemia occurring in some patients. Whether this reaction represents a form of true hypersensitivity or not is open to question at present.

The only case of skin hypersensitivity to this compound previously reported was presented by Hall² before the British Dermatological Society in 1899. The patient was Scotch, aged thirty years, a research worker in a chemistry laboratory, and first noticed a mild eczema on his fingers in 1894. When he rested from his work, the rash cleared up; when he returned to work in the laboratory, it returned with a constantly increasing severity. He was using phenylhydrazin in a research problem at the time but did not associate that drug with the eczema until a year later when he spilled some on his hand. In two hours he developed an urticarial reaction over most of his body and extremities. He then turned over the work associated with the phenylhydrazin to an assistant. He became progressively sensitive until, according to Hall, on one occasion, when his assistant, who had been working with phenylhydrazin hydrochlorid, came a distance of a mile to see him in his home, he had a severe recurrence of his eczema. The progressive severity of his attacks may be significant from the viewpoint of prognosis in the present case.

Contact with this drug is not limited to a few research workers in the field of medicine today, since practically all freshmen in medical schools use it in the study of the osazones of the various sugars. The occurrence of individuals with a hypersensitivity to it must be rare inasmuch as there appears to have been no cases reported during the present century.

Case Report. The patient, male, aged twenty-three years, a medical student, first noticed a mild pruritus of the skin of the thumb and index finger of the left hand, with multiple minute vesicles and diffuse redness over the same area—February 17, 1929.

The next day, February 18, several small red areas, the largest 15 cm. in diameter, appeared on the palmar surface of the hand around the base of the thumb and index finger. Pruritus of the skin of the right thumb and index finger was also noticed. A diagnosis of "dermatitis, probably ringworm" was made by a dermatologist, and a solution of camphor and iodine was prescribed for external application. In the afternoon, the patient worked in the chemical laboratory of the medical college which he was attending.

February 19. The following morning, the eruption was much more severe and it was accompanied by a moderate swelling of the palm, thumb, index finger and ring finger of both hands. Again the patient visited the same dermatologist who diagnosed the condition as "dermatitis, probably of poison ivy or primrose poisoning."

February 21. Both hands, including the palms and all of the fingers, except the fifth finger of the right hand, were so swollen that it was impossible to bend any of the finger joints. The fingers actually appeared to be twice their normal size. There were many broken vesicles with serous contents present and desquamation was moderately severe. Throbbing pains were constant in both hands which incapacitated the patient temporarily. An examination of the urine revealed nothing abnormal. Wet dressings of lead acetate and alcohol were continuously applied without apparent effect.

February 24. A mixture of bismuth subcarbonate, zinc oxide, zinc stearate, glycerin, and carbon detergent, was applied. The condition subsided so rapidly at this time that it seemed doubtful that the relief could be attributed to the medication.

February 27. Both hands had returned to their normal status. The skin appeared to be clear except for a slight residual desquamation. It was then realized that each period of time spent in the chemical laboratory had been followed by an acute exacerbation of the condition. The patient had been an industrial chemist before entering medical school, so it seemed probable that the cause of his hypersensitivity would be found in some element or compound which he was then using but had not used in his previous work.

In the laboratory he was studying the osazones and using in this work phenylhydrazin hydrochlorid (1 part) with sodium acetate (2 parts).

Experiments. This fact suggested a series of experiments with two subjects:

A. To determine whether the patient was hypersensitive to phenylhydrazin hydrochlorid plus sodium acetate.

B. To determine what fraction or group of fractions in this compound might be the exciting factor or factors of this hypersensitivity.

1. A few crystals of phenylhydrazin hydrochlorid (1 part) mixed with sodium acetate (2 parts) were rubbed on the volar surface of the left forearm over an area of 1 cm. in diameter. Seven hours later there was marked redness over that area, and at the ninth hour some swelling was noted. Nineteen hours after exposure the redness had extended for a distance of 3 cm. in all directions from the original area and a sharply demarcated elevation of about 2.5 mm. was present over the entire area. Pruritus was marked at first but disappeared after about four days. This was repeated three times with similar results.

2. Phenol (95 per cent) was applied to the skin; until small vesicles appeared, to determine whether the phenol radicle might be the source of the irritation. No reaction followed except for the above-mentioned vesicles which quickly healed.

3. Sodium acetate in powdered form was rubbed in over an area

of several square centimeters on the volar surface of the arm. No skin reaction followed.

4. Hydrochloric acid, concentrated, was applied over an area 1 cm. in diameter on the volar surface of the forearm. No evidence of hypersensitivity was noted.

5. Pure hydrazin hydrochlorid was applied over an area 1 cm. in diameter on the volar surface of the forearm. No evidence of hypersensitivity was noted. This was repeated twice with similar results.

6. Phenylhydrazin hydrochlorid was applied over an area 1 cm. in diameter on the volar surface of the forearm. Seventeen hours later there was a mild pruritus, and redness of the skin over an area slightly larger than that exposed. The reaction in this experiment was much more mild than those in Experiments 1 and 7.

7. Phenylhydrazin hydrochlorid (1 part) plus sodium bicarbonate (2 parts) was applied over an area 1 cm. in diameter on the skin of the volar surface of the forearm. Pruritus and redness appeared within three and a half hours. The course was similar to that in Experiment 1, the skin returning to a normal appearance in four days.

8. Pure phenylhydrazin base (98 per cent) fluid was rubbed with cotton over an area of skin 1 cm. in diameter. No evidence of hypersensitivity was noted.

9. This experiment was repeated rubbing the solution in with sand to scarify the skin. Again there was no evidence of hypersensitivity.

10. Following some of the reactions above described, the mixture of bismuth subcarbonate, zinc oxide, zinc stearate, glycerin, and carbon detergent was used locally. At other times, it was not used. No difference was noted in the subsidence of symptoms.

Conclusions. 1. A case of skin hypersensitivity to phenylhydrazin hydrochlorid is herein presented.

2. The reaction manifests itself in the form of pruritus, swelling, vesicle formation, pain, and desquamation locally and in surrounding areas—never thus far as a generalized reaction.

3. The skin reactions were much more prompt in appearance, and more severe when the phenylhydrazin hydrochlorid was mixed with two parts of sodium acetate or sodium bicarbonate thus rendering the reaction markedly alkaline.

4. The application of phenyl, sodium acetate, hydrochloric acid, pure hydrazin hydrochlorid and pure phenylhydrazin base in fluid form to the skin, with and without excoriation, by means of sand, failed to produce any evidence of hypersensitivity.

5. The patient is not hypersensitive to any of the fractions of the compound phenylhydrazin hydrochlorid but only to the compound as a whole and these reactions can be accentuated by the addition of certain alkalies not in themselves responsible for the reactions.

6. Medications locally applied did not appear to influence the course of the reactions.

NOTE.—We wish to thank Dr. John A. Killian and Dr. Stanley R. Benedict for their kind aid and advice during this study.

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FURTHER STUDIES IN THE DIETARY CORRECTION OF OBESITY.

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IN the treatment of obesity, it is necessary to appreciate the fundamental facts of the metabolism of the obese and to adapt the generally accepted principles of dietetics to meet the needs of this physiologic anomaly. Unfortunately, many of the basic facts are not well established. The dietetic study of obesity here reported, an elaboration of those already published (see this Journal, 1929, 177. 339), has been carried out in an effort to examine some of these points.

The excess weight in obesity represents chiefly fatty tissue, composed for the most part of fat and water. Stored water may be removed from the body by several channels; insensible perspiration, sweat, feces and urine. In the light of present knowledge, however, the sole mechanism for the removal of fat is by the natural process of combustion which follows upon the mobilization of the stored material by a reversal of the storage process. As the rate of fat deposition is controlled by the excess of food intake over the body needs, the rate of lysis and combustion of fat is governed by the excess of energy output over intake. The rate of weight loss is, therefore, influenced by variations in both intake and output. The two factors are interdependent, the output being very definitely

influenced by the intake. In the treatment of obesity, the attention must then be focused neither upon the intake nor upon the output but upon the difference between the two. The goal is not a low intake *per se* nor a high output but rather the lowest intake at which can be preserved so high an output that the maximum possible difference between intake and output is secured. Starvation, even though not contraindicated for other reasons, does not meet the situation because it produces such a depression in basal and total metabolism that we by no means approach this maximum difference.

In establishing the essential components of the diet, the protein requirements demand careful consideration. The studies on undernutrition of many investigators, among whom may be mentioned Benedict,¹ Lusk,² suggest that the deficiency of nitrogenous food with its consequent negative nitrogen balance is one of the principal factors associated with the concomitant depression of metabolism. There must be in the diet, therefore, enough protein to maintain nitrogen balance and prevent this starvation depression of metabolic level. It must also be remembered that, as Woodyatt³ and others have indicated, a transformation of protein into available glucose in the body can occur in times of carbohydrate stress. Finally, in the construction of any diet of a restrictive type, the biologic value of the proteins employed becomes important. The evaluation of these principles is not a simple matter. Arbitrarily, therefore, a standard of 1 gm. protein per kilo of ideal weight was adopted for the present study, the protein being selected only from sources with the highest biologic values.

The amount of carbohydrate is one of the radical changes in the present diet as compared with that previously described.⁴ The earliest teaching, dealing with carbohydrate metabolism, employed the apparent principle that the combustion of fat and glucose are interdependent in a definite numerical ratio. The evidence also seems to show that fat is not available as a source of glucose.⁵ Furthermore, the work of Woodyatt,³ Shaffer⁶ and others has taught us to recognize antiketogenic factors other than the carbohydrate of the diet and to deal with the glucose equivalents. Evidence which is now accumulating from various sources questions a fixed ratio for the combustion of glucose and fat molecules. These conceptions have influenced us to abandon the method previously employed of supplying carbohydrate in an amount which maintains a theoretical ketogenic-antiketogenic ratio of $1\frac{1}{2}$ to 1. The first diet used in this series of cases called for no carbohydrate whatever for the purpose of known carbohydrate metabolism. Later diets contained carbohydrate up to a total of 20 gm. in order to obtain a desired effect upon the nitrogen balance.

The fat in the molecular mixture which the body burns is derived almost entirely from the body stores.

If the metabolic factors above presented were the sole considerations, the diet would contain protein requirements with only the inseparable carbohydrate and fat. The vitamin content of the food must, however, be kept in mind. Weight was given to the reasonable assumption that human fat compares favorably with other animal fat in its capacity to store the fat-soluble vitamins. Accordingly, our patients received definite amounts of actively growing yeast, orange juice and whole milk. These amounts were small but materially increased the carbohydrate and fat values of the diet.

An adequate salt supply must be given. Quantitative data on this subject are not too reliable, but the preference is to err on the side of an excess rather than a deficiency. Kalak water contains most of the necessary cations and anions. It is also alkaline, a factor which was considered at the outset as of importance in dealing with potential acidosis. More recently, we have used with good results, Tyrode's solution without glucose.

A diet constructed on the basis of the protein, vitamin and salt requirements made possible an average daily intake of less than 360 calories. It was thought this diet would provide the lowest possible intake consistent with the maintenance of a normal basal metabolic rate and normal daily activities with their concomittant extra demand for energy expenditure. Thus, the maximum difference between intake and output would be obtained and the most rapid loss of weight, without injury to the organism, result.

The menu, which was used principally at the outset, was composed of fresh meat and egg white. Approximately 100 gm. of lean steak was the backbone of each of the two largest meals. When necessary, fresh fish was given at intervals. Egg white was employed to balance the daily protein requirement. This was perhaps more desirable than the meat in view of the presence of fat and protein in almost equivalent amounts in even lean meat. On alternate days, the patient received either 100 cc. of whole milk or 100 cc. of orange juice and 50 cc. of actively growing yeast. One glass of Kalak water was given three times a day. The later diets contained carbohydrate sufficient to make a total of about 20 gm. This increment was supplied in the form of 5 per cent vegetables.

The question of how much water should be ingested daily has not been definitely answered as yet. We asked the patient to drink at least 2500 cc. a day. At times, the daily intake reached 4500 to 5000 cc., due to the enthusiasm of the patients.

This report deals with 13 patients who were dieted in the hospital under the especially rigid conditions of the metabolic service. At the inception of the dieting period, the average weight of the patients was 259 pounds (maximum, 427; minimum, 180). The average duration of the diet was fifty-nine days. The average final weight was 224 pounds. The average weight loss was 35 pounds in fifty-nine days (maximum, 104 pounds in one hundred and seventy-

TABLE I.

EVANS: OBESITY

TABLE I.

Case No.	Age.	Preliminary diet.			Restricted diet.								
		Initial weight, lbs.	Calories.	Duration days.	Weight loss, lbs.	Weight at outset, lbs.	Duration days.	Final weight, lbs.	Weight loss, lbs.	Calories.	Protein, gms.	Carbo-hydrate, gms.	Fat, gms.
9026	60	359	3690	4	5	354	178	268	86	328	53	17	7
9567	58	432	2260	5	5	427	176	323	104	358	65	14	5
9601	33	195	2870	4	0	195	45	166	29	353	58	12	8
2379	24	220	218	47	194	24	310	46	14	7
4140	39	275	2850	6	3	272	25	256	16	319	55	11	8
1223	27	234	2630	2	0	234	14	217	17	337	60	9	7
4242	35	181	2900	2	1	180	13	171	9	303	50	10	7
753	50	207	1450	5	4	203	8	198	5	375	62	18	7
10,007	43	191	191	14	178	13	353	59	12	7
8127	45	248	240	51	227	21	395	63	17	9
8890	39	240	228	47	210	30	457	70	21	10
8511	52	228	377	50	203	25	369	63	10	9
7466	39	378	1868	7	1	377	97	305	72	382	56	21	8
Average	42	261	2570	4	2	259	59	224	35	357	58	14	8

six days; minimum, 5 pounds in eight days). The average rate of weight loss was, therefore, slightly less than 0.6 of a pound per day.

The average figures for the diet provided were 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat—a total of 360 calories. Attention should be called to the fact that nearly two-thirds of the total exogenous calories were protein. These figures represented the food supplied but by no means indicated the mixture actually metabolized. This must include the body substance, chiefly fatty tissue and protein tissue, which was burned.

The loss of protein tissue may be estimated from a study of the relative intakes and outputs of nitrogen during the dieting period. The nitrogen balance of several of these patients has been carefully determined and constitutes the subject of a separate report.⁷ Briefly, the evidence at hand indicates that during the first three weeks of rigid dieting, patients may lose nitrogen to the extent of 40 to 50 per cent above the nitrogen intake. The addition of 10 to 15 gm. of carbohydrate to the diet causes an abrupt drop in the nitrogen output and the attainment of a permanent nitrogen balance without the alteration of the nitrogen intake. On the most recent patients, an attempt was made to prevent the preliminary loss of nitrogen by adding this carbohydrate to the initial diet. We have so far been unable to prevent this early loss but have strikingly reduced the duration of the loss period to two weeks.

It is, therefore, obvious that protein tissue was lost to some extent by all of these patients. There can, however, be no question that fatty tissue was the greatly predominant source of weight loss. In the absence of data regarding the exact nitrogen loss on several of these patients, we have omitted this protein tissue loss from the calculation of the approximate average metabolic mixture which the body actually handled.

The average food intake, as recorded above, was 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat. If we assume that the body weight loss was fatty tissue containing 14 per cent water, the observed weight loss, 0.60 pounds or 270 gm., is equivalent to 232 gm. of dry fat. The body actually handled, therefore, approximately 58 gm. of protein, 14 gm. of carbohydrate but 240 gm. of fat. The glucose equivalent was 72, most of which came from protein and less than $\frac{1}{5}$ from carbohydrate in the diet. The carbohydrate intake was accordingly no index of the antiketogenic properties of the metabolic mixture. The ketogenic-antiketogenic ratio was 3.4—certainly a high ratio and still there was no evidence of clinical acidosis. A further support of this method of calculating the metabolic mixture is obtained by noting that the total daily calories of this mixture was 2520, which differs but slightly from the average caloric value of the selected diet on admission.

It is noteworthy that of a total daily energy exchange of approximately 2500 calories, only 360, or one-seventh of the total, was sup-

plied as food. The remaining six-sevenths came from the energy reserves. For weeks these patients maintained health and mental and physical vigor on an intake of less than 3 calories per kilo per day. Two patients whose weights at the beginning of the restricted diet were 354 and 427 pounds respectively, took less than 2 calories per kilo per day for six months.

It is necessary to emphasize the fact which has been reported by many that although the patient may burn 250 gm. of her stored fat per day she does not necessarily lose weight every day. The curve of the daily weight change is a series of ups and downs with frequent periods of no apparent weight change. As has been repeatedly demonstrated, these irregularities are intimately associated with the storage and release of relatively large quantities of water. The influence of this phenomena on the true weight loss is minimized if the period of observation is sufficiently long. It is possible to predict with gratifying precision the weight to be expected from the deficiency in exogenous calories.

Drugs and endocrine preparations were not used. Any preparations of value must remove fat by hastening its combustion by increasing the metabolic level. Thyroid is contraindicated because the basal metabolism of the obese is already 20 to 50 per cent above the ideal level.⁸ The various ovarian and panhormonic preparations have no demonstrable influence on the metabolic rate.⁹

The clinical side of the picture is encouraging. In spite of the early negative nitrogen balance, these patients were apparently not starved physiologically. The personal efficiency was greatly increased. All varieties of minor aches and pains disappeared. There were no observed complications attributable to the diet. The opinion that there is no primary deficiency in the diet rests upon the careful observations of the two patients who for six months carried on the diet under close observation in the metabolic pavilion.

The contraindications to this dietary régime seem to be chiefly the lack of courage of the physician. It has, however, not yet been used on patients who were not in residence in the hospital and who were not primarily problems in obesity.

For some time we have been intrigued by the statements of fat people that they eat little or nothing and yet do not lose weight. An attempt has been made to evaluate these impressions by having each new patient eat for three or four days what she ordinarily ate at home. The intakes were carefully weighed. Eight of the patients considered here averaged 2570 calories a day for four days (maximum, 3690; minimum, 1450). But what is more significant, they lost weight, averaging 2 pounds per person, in four days on this intake. In view of a weight loss on this intake, one wonders what must have been the intake at home on which the patient gained weight.

The question is frequently raised as to the permanence of the

weight losses obtained. We believe that no person will gain weight if his energy intake does not exceed his output. The hope for permanence of the reduced weights, therefore, depends upon the development of entirely new dietary habits in the individuals during their periods of strict observation.

In the absence of convincing evidence pointing to a metabolic economy in the obese, one is forced to the opinion that fat deposits result solely from an excess of energy intake over energy output. Conversely, the only method available for the dissipation of this extraordinarily efficient energy reserve is its combustion in the usual manner. The rate at which this combustion can occur is determined by the difference between the caloric intake and caloric output.

The diet described is designed to supply the smallest possible intake while still preserving the maximum output. It consists of sufficient protein to maintain the body requirements plus enough vitamins and salts to prevent the occurrence of the complications which result from deficiencies. The only carbohydrate and fat given are those which are required by the protein and inseparable from accessory food substances. This made possible diets containing but 360 calories per day.

By the use of this diet on 13 patients, a uniformly satisfactory loss of 0.6 pound per day for fifty-nine days was secured. Despite an early negative nitrogen balance, lasting for some weeks, no untoward reactions were observed even after six months rigid adherence to the régime. Although 0.6 of a pound a day seems a very small amount to a patient who has been advised to lose 50 or 100 pounds, any method which will consistently remove four pounds a week and at the same time actually increase the vitality and sense of well being of the subject is worthy of careful investigation.

Summary. 1. A reduction diet is described which supplies only the body requirements of protein, vitamins and salts.

2. The diet averages 360 calories per day which are derived from 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat.

3. Thirteen patients showed an average weight loss of 0.6 of a pound per day for fifty-nine days.

4. Clinically, the patients were greatly benefited and showed no untoward reactions in spite of: (1) an early nitrogen loss; (2) a theoretical ketogenic-antiketogenic ratio of 3 to 4.

5. Patients have been maintained on this rigid diet without complications for six months.

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BRONCHOLITHS.*

WITH REPORT OF FOUR CASES.

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SINCE the time of Aristotle calcareous material expelled from the lower respiratory tract has attracted attention. The expectorated material has received many designations, for example, pneumolith, pulmolith, lung calculus or stone, broncholith, bronchial calculus or stone. Apparently in most instances they refer to the same thing. The term broncholith should, perhaps, apply only to those calculi arising from a deposit of calcium salts in the bronchus, for example, in a pocketed bronchiectasis or those arising from a sequestrum of bronchial cartilage acting as a matrix. However, as most authors have used the term broncholith, I have chosen this as the title, in spite of the fact that the majority of bronchial or pulmonary calculi have their origin in the lung tissue outside the bronchus proper.

Paulalion,¹ in his thesis before the Paris Academy in 1891, gives a full discussion of the condition and has been much referred to in the recent literature on the subject.

Wells² shows the close analogy between calcification and ossification. His opinion, which is concurred in by Harbitz,³ is that the processes differ only morphologically, the calcium deposit in calculi being at first in granular form but that it later may become homogeneous through fusion. Wells states "That within such deposits there are usually no living cells and no further change takes place unless it be absorption or the addition of more calcium salts." Whereas, in normal ossification the homogeneous calcium deposits

* Read before the American Climatological and Clinical Association, May 4, 1929.

are closely related to the living cells which not only determine the form of the deposits, but are also able to dissolve the insoluble salts and to cause their deposition as may be needed.

Chemically, with few exceptions, these pathologic deposits have been found quite the same as that of normal bone, 85 to 90 per cent calcium phosphate and 10 to 15 per cent calcium carbonate. Wells quotes Poscharissky as having examined calcified nodules from the lungs of 28 persons and finding bone in 17 (60 per cent). Osler⁴ mentions osseous calcification as arising from the bronchial cartilages following prolonged suppuration, as in bronchiectasis or pulmonary tuberculosis; from old pleurisies; from the walls of abscesses; in sclerosis and in true osteotomata and very rarely in tracheo-bronchial mucous membrane, the seat of old disease.

In another article Wells⁵ discusses metastatic calcification accompanying destructive bone diseases, for example, osteomalacia, bone tumors, either primary or secondary and leukemic conditions. In these diseases there is rapid liberation of calcium salts into the blood stream and, as quoted by Harbitz,³ Virchow showed, in 1885, that certain organs and tissues are predisposed to calcareous infiltration, namely, the lungs, the endocardium of the left ventricle, the pulmonary veins, the gastrointestinal mucous membrane and the kidneys. Calcium salts, according to Wells,⁵ are absorbed to a greater amount than can be held in solution by the arterial blood, so that no calcium is found deposited in the right side of the heart, but after the blood has passed through the lungs and lost a large part of its carbon dioxid, the calcium salts are precipitated in the pulmonary veins, the left heart and taken up by adjacent tissues. Watt,⁶ concurs with the theory of Wells,⁵ that it is probably loss in the carbon dioxid content of the blood which permits the precipitation of the calcium salts in the tissues. There has been no cellular action demonstrated which can be responsible for the deposition of the salts. He further points out that calcium deposits in tissues have no organic structural framework nor is there any fibrous tissue capsule surrounding them.

The deposition of calcium salts in the bronchopulmonary lymph nodes is probably a process of filtration alone. (Bloor.⁷)

Tuberculosis has been regarded as the disease in which broncholiths are most apt to arise. Flint,⁸ in reporting 2 cases, says, "The histories are consistent with the doctrine which holds pulmonary calculi to be obsolete tubercles," and many authors since are of the same opinion.

Jackson⁹ divides lung stones into three classes: "(1) True calculi; (2) calcium deposits in tissues that sloughed loose and gained entrance into the bronchus; (3) pneumoconiotic, silicotic or anthracotic material that has loosened by disintegration or suppurative liquefaction of the encasing tissues."

In the routine study of lungs by Roentgen ray one is struck by

the frequency with which calcareous deposits are seen in the pleura and in the lung structure, particularly in the region of the hilum and in an advanced tuberculous process of long duration. However, the occurrence of inflammatory reaction leading to ulceration into a bronchus is a relatively rare occurrence if one is to judge by the number of cases reported in the literature. Just why calcified masses should in most instances remain silent throughout life and in a very small per cent become freed and expelled, is not known.

Samuel West,¹⁰ in speaking of the frequency of broncholiths, says he knows of only one set of figures dealing with this phase of the subject which gives the incidence as 16 in 1000 cases of tuberculosis. He adds that he thinks this an unusually high percentage. He gives a list of 15 cases which he found recorded in 1902, each reported by a different observer.

In a review of the English language literature since 1900 I have found 18 cases reported. Of this number, two authors, Pritchard¹¹ and Lyter,¹² report 2 cases each, the others reported a single case, Jackson⁹ (apparently this same case is reported¹³), Pratten,¹⁴ Benjamin and Mollison,¹⁵ Friedman,¹⁶ Maytum,¹⁷ Vinson,¹⁸ Shasted,¹⁹ Cole,²⁰ Stivelman,²¹ Fox,²² Elliott.²³ Of these 18 cases, 7 occurred in tuberculous patients and 8 in apparently nontuberculous.

Jackson,²⁴ in his book on bronchoscopy, says: "Broncholiths have been found and removed bronchoscopically in a number of instances at the Bronchoscopic Clinic," but he does not state the incidence, merely mentioning 3 specific cases, which are included above.

Pritchard¹¹ encountered 2 instances of broncholiths among 7000 patients studied at Battle Creek Sanatorium.

Stivelman²¹ reports only 1 such occurrence in "5000 cases of tuberculosis personally observed." Curiously enough, the 4 cases I have to report were seen in the past six years. The incidence seems above normal, as the number of cases seen by me in the past eighteen years could hardly exceed 5000, both tuberculous and nontuberculous.

The stones vary in size from granular particles as described by Jackson²⁴ to that reported by Fredault,¹⁰ weighing 139 gr.

They are usually grayish-white in color, gritty and hard, but sometimes are putty-like in consistency. They are usually rough in outline and when multiple may be faceted.

The calculi may be single or there may be a large number expectorated from time to time. Boerhaave's⁴ case of Sebastianus Vailantius, the famous botanist, who expectorated 400 calculi before he died of "phthisis calculosa," and Flint's⁸ case of a farmer who expectorated more than a pill box full and who, thirteen years later, was in good health, and the case reported by Portal,¹⁰ who expectorated 500 stones, seem to have been the most prolific. One of Pritchard's¹¹ cases expectorated 40 to 50 calculi during four days.



FIG. 1.—Case III. At the end of the white arrow, in the right hilum region, is seen a small calcified mass.



FIG. 2.—Same patient as in Fig. 1, four months later, showing disappearance of calcification at end of arrow.

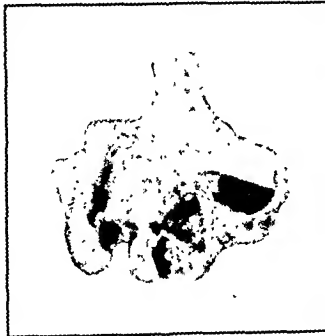


FIG. 3.—Photograph of broncholith expectorated by Case III. Magnified 5 times.



FIG. 4.—Case IV. Lipiodol shows normal bronchial tree in the right middle lobe and the descending trunks of the left. At the end of the arrow, above the right hilum, is seen a large calcified area.

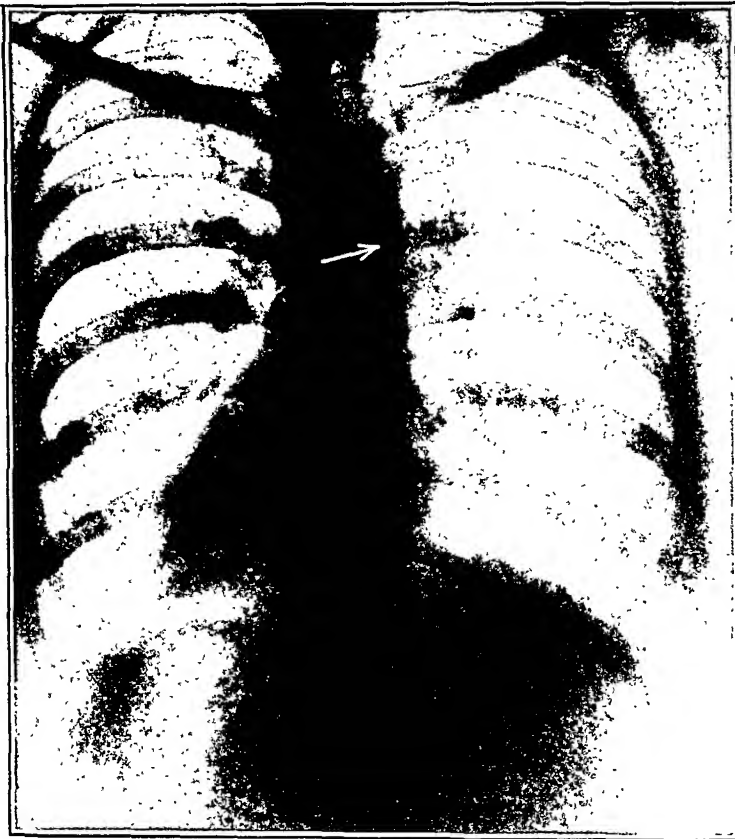


FIG. 5.—Same patient as in Fig. 4. At the end of the arrow is seen an area of pneumonitis in film taken five days after expectoration of broncholith.



FIG. 6.—Same patient as in Figs. 4 and 5, one month later. Shows pneumonitis having cleared and the area of calcification disappeared entirely.

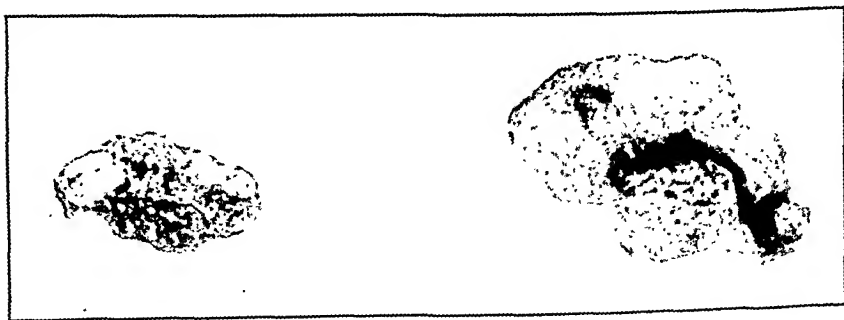


FIG. 7.—Two broncholiths expectorated by Case IV. Magnified $3\frac{1}{2}$ times.

The symptoms of broncholithiasis vary with the size and shape of the stone from an unconscious raising of the stone with sputum, when the hard substance is discovered in the mouth; to the very severe "stone asthma" or bronchial colic, in which there may be felt intense pain beneath the sternum accompanied by a sensation of impending suffocation.

The expulsion of the stone, however, is usually preceded and accompanied by a severe paroxysmal cough and frequently is accompanied by streaked sputum or hemoptysis.

Elevation of temperature, malaise and prostration may be present preceding the expulsion, but in most instances recorded the symptoms were largely relieved shortly after the stone was expectorated.

In several cases reported the paroxysmal cough preceded the expulsion of the stone by several weeks and the bronchoscopic removal of broncholiths in cases of bronchopulmonary suppuration by Jackson^{9, 24} and Vinson¹⁸ emphasize the serious results consequent upon the retention of calculi in the bronchi—bronchiectasis, lung abscess or empyema.

In tuberculosis as well, one wonders if there may not be an infrequent connection between the posthemorrhagic pneumonia or a pneumonic spread and a possible retained broncholith.

Two of the 4 cases reported below occurred in advanced tuberculosis. Cases III and IV are unusual in the fact that the calcareous deposit was plainly visible in an Roentgen ray film before the broncholith was expelled and had disappeared in subsequent film. Jackson¹³ reports 1 similar case.

Case Reports. CASE I.—P. Y., male, aged thirty-six years, a traveling salesman, died on November 7, 1925, of advanced tuberculosis, having been ill with tuberculosis seven years prior to death. He developed a large cavitation in the upper lobe of both lungs and spat up four to five cupsful of sputum daily. During the last two years of life he expectorated many small calculi without symptoms. Their nature was discovered when the hard substances reached the mouth. Other larger ones were accompanied by considerable bronchial colic and when this occurred the sputum was always blood tinged. None of these calculi were preserved, but several, from $\frac{1}{2}$ to $\frac{3}{4}$ cm. in diameter, were seen by the author.

CASE II.—Mrs. J. M., aged thirty-one years, married, was seen on December 8, 1921, with acute pleurisy and a moderately advanced lesion in the upper left lobe. She went to a health resort in 1922, where she remained until December, 1929, and returned home. She expectorated 1 small stone in 1919, then none until the fall of 1924, when she raised 1, more or less circular in shape and 1 cm. in diameter, and daily the next three weeks raised smaller ones, 2 or 3 a day, and again in the fall of 1925 raised 1, $1\frac{1}{2}$ cm. in diameter, followed by 6 or 8 smaller ones in the next three or four days. In 1929 she raised 1 on March 11 and 1 on March 12, both about $\frac{1}{2}$ cm. in diameter. She has never had bronchial colic, but the sputum is frequently blood tinged. The stones are not always accompanied by streaks, but are usually embedded in heavy, mucopurulent sputum. She expelled, all told, from 50 to 60 stones.

None of these stones were preserved. The disease has progressed and she now has extensive involvement in both lungs with cavitation.

No history of stone spitting was obtained until the specific question was asked, "Have you ever raised any stones?"

CASE III.—E. A. S., female, aged fifty-two years, single, a teacher, has had the following disorders: In 1915 her right breast was removed for nonmalignant tumor; left ovariectomy and appendectomy in 1920; in 1923 tonsillectomy; iritis off and on since 1922. In October, 1925, lobar pneumonia followed by interlobar empyema with operation, October, 1925. Recovery was slow. She has had many negative sputa examinations. The urine is normal. In August, 1928, during a violent coughing attack, she raised a small stone followed by a small quantity of foul-tasting sputum. This was followed by a rather severe bilateral bronchitis, which continued until the latter part of October. No more stones were expelled and since that time she has been in excellent health.

In this case a film taken, October 2, 1928 (Fig. 4), showed the disappearance of a calcified area which was noticed in film of June 14, 1928 (Fig. 3).

The calculus was saved and is shown in Fig. 5. It is $\frac{1}{2}$ cm. in diameter, hard and very rough.

CASE IV.—F. V., female, aged fifty-four years, single, a teacher, was first seen on April 8, 1926. Her father died at the age of thirty-seven years of rapid tuberculosis, when the patient was two and a half years of age. Her mother died at the age of seventy-five years from a heart attack.

At the age of nineteen years the patient had an acute nephritis and was ill for about a year; also an operation for gastric ulcer in 1916; tonsillectomy in 1918. In 1922 she had an attack of grippe and was in bed three weeks and away from work six weeks. Following this attack she continued to cough, raising a cupful of thick, yellow sputum daily, which was negative for tubercle bacilli. There were many râles in the right middle lobe, with feeble breathing. Lipiodol injected showed normal bronchial trunks. Left antrum was found to be filled with pus and was cleared by irrigation. Following this, cough disappeared and she was perfectly well from August 1, 1926, to July 1927. On July 15, 1927, she had general malaise, a temperature of 100° to 101° F. and began coughing. The temperature continued elevated and the cough persisted in paroxysms, until, on July 20, during a violent coughing attack, she raised two pieces of calcified material in thick, yellow, blood-tinged sputum. Cough continued for about a month, when it again disappeared. A Roentgen ray made (Fig. 7), July 20, 1927, showed an area of cloudiness above the right hilum and the disappearance of a calcified mass which was noticed in previous films. In a film made, August 13, 1927 (Fig. 8), the area of pneumonitis had disappeared and she has had no further attacks. The two calculi were preserved and are shown in Fig. 9. One was 1 cm. in diameter, the other $\frac{1}{4}$ by $\frac{1}{2}$ cm., both very hard and irregular and each faceted.

Summary and Conclusions. 1. The occurrence of bronchololiths was known and reported by the oldest medical observers. The stones probably originate most frequently in an obsolete tuberculosis of a bronchopulmonary lymph node in or near the hilum.

2. In a fairly thorough review of the literature in the English language since 1900, 18 cases were found in addition to the 15 cases found by West in 1902—4 more cases are added in this paper, making a total of 37.

3. The condition probably is more frequent than reported cases would lead one to suppose as the expectoration of stones may be easily overlooked in history-taking, for example, Case II reported above.

4. The erosion of a calculus into a bronchus may produce serious results should the stone remain in the bronchus. Perhaps such an occurrence may occasionally account for a posthemorrhagic spread in tuberculosis as well as producing a bronchiectasis, lung abscess or empyema.

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ALLEGED MENSTRUAL FEVER IN PULMONARY TUBERCULOSIS.

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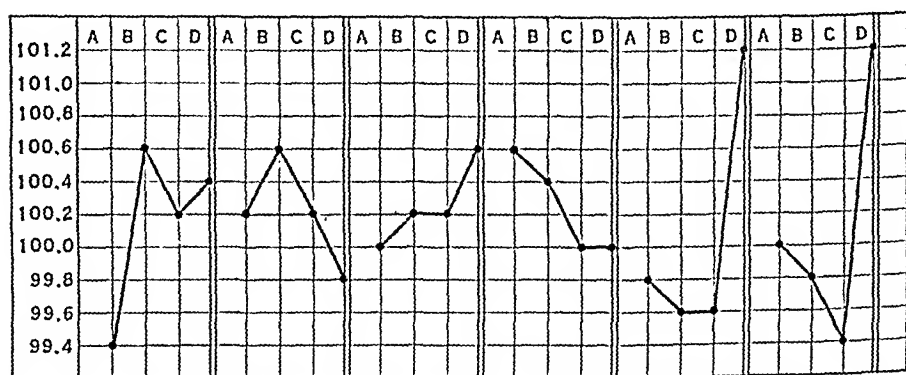
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ELEVATIONS of temperature in tuberculous females are claimed to have a cyclic association with menstruation. It is maintained that such cyclic fever can be identified as a characteristic entity so as to have a diagnostic and prognostic significance.^{1,2} Premen-

strual, menstrual, postmenstrual and intermenstrual fever have been described.^{3,4,5,6} Kessel,⁷ in contrast, observed that in 96 of 100 cases no rise in temperature occurred within five days preceding the onset of the menstrual period. Welch⁸ studied 500 cases and observed a depression in temperature during menstruation.

The identity of a characteristic cyclic type of fever in pulmonary tuberculosis is at variance with the irregular course of the temperature observed in the disease. In order to arrive at exact conclusions an examination was made of the temperature charts of 100 tuberculous females, in all stages of the disease, who had been in this institution for six or more months and who had an equal number of normal menstrual cycles. Six months was chosen as a minimum period of observation because, as will be shown later, only by observing patients over at least such an interval can conclusions of a diagnostic value be obtained. For convenience the menstrual cycle was divided into four periods: Premenstrual, seven days before menstruation; menstrual, the actual flow; postmenstrual, seven days after menstruation; intermenstrual, the time between the post and premenstrual periods. The highest temperature during each of these respective periods for six successive months was charted, as shown in the accompanying chart. Such a scheme enables one to perceive not only fever but slight elevations of temperature which might have significance when relatively compared. All temperatures were taken per rectum.



Six consecutive temperature curves with relation to menstruation in the same individual: A, premenstrual period, seven days before menstruation; B, menstrual period, actual flow; C, post menstrual period, seven days after menstruation; D, intermenstrual period, time between post- and premenstrual period.

The temperature curves showed no regular changes associated with the menstrual cycle which could be identified as a characteristic entity. It is true that a given patient may have a decided rise of temperature at most premenstrual periods for several consecutive months. From this we could erroneously conclude that this is an

example of premenstrual fever, but this same patient would have similar elevations at various other times during the same month. Likewise, analogous curves with the stress of changes upon the menstrual, postmenstrual and intermenstrual periods were frequently noted. Moreover, very often a patient would have a rise of temperature only at some one period for a few consecutive months, but over an observation of many months this apparent cyclic rise disappeared. Thus in chart the highest temperature for two consecutive months occurred during the menstrual period, yet during the remaining months of her stay at the sanatorium this high temperature was present at various other periods. This emphasizes the necessity of observing a patient for a minimum of six months. Conclusions otherwise would be deceptive.

It is thus easy to observe that tuberculous patients show rises of temperature at some arbitrary time during the month, either at the premenstrual, menstrual, post or intermenstrual period, ignoring the fact that they show similar rises at other intervals even during the same month. To state then that such a rise, because it occurs at that period, is a periodic rise and is diagnostic of tuberculosis is an erroneous conclusion. For a rise of temperature to be cyclic it should occur solely at some one interval and only at that interval over an observation of several months. Dluski⁹ found no influence on temperature during menstruation in 56 per cent of 300 tuberculous women examined for several months. In others the temperature proved extremely variable during menstruation even in the same women. There was no special type, and his experience does not indicate that fever during menstruation is necessarily a sign of tuberculosis. Wiese¹⁰ studied the temperature curves of 500 definitely diagnosed tuberculous women under sanatorium treatment. He concludes that there is no type nor regularity of thermic disturbances associated with menstruation.

We were unable to obtain data of a prognostic value from this study. Except in patients who have a marked elevation of temperature over a continued period, it is extremely difficult to make a prognosis in phthisis from an examination of the temperature chart alone, since the prognosis depends on numerous factors other than the temperature.

Assuming that fever associated with menstruation could be identified as an entity in tuberculosis, to have any diagnostic value it should be characteristic of the disease. But even normally physiologic rises of temperature are attributed to menstruation.^{11,12} Moreover, in numerous diseases, such as scarlet fever, typhoid fever, rheumatic fever, chlorosis, premenstrual fever has been known to occur.^{13,14,15}

Conclusions. Though catamenia may be associated with a rise of temperature in tuberculous patients, this phenomenon has no diagnostic or prognostic value because:

1. Fever associated with the menstrual cycle has been noted in normal women and in numerous diseases other than pulmonary tuberculosis.

2. It cannot be identified as a characteristic entity in tuberculous individuals since fever occurs at different periods with relation to menstruation in different tuberculous females, or even in the same patient if examined over a properly long period.

3. A diagnosis and, except in characteristic instances, a prognosis in pulmonary tuberculosis cannot be made from an examination of the temperature curve alone.

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REVIEWS.

ROENTGENOGRAPHIC TECHNIQUE. By DARMON ARTELLE RHINEHART, A.M., M.D. 388 pages; 159 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$5.50

THE author of this textbook has covered his problem admirably. The book contains 20 chapters dealing with electricity and electric current, Roentgen ray machines, dark-room equipment and technique, and basic roentgenographic technique with various experiments to illustrate the value of such technique. He illustrates the position that will demonstrate the parts to best advantage. The author not only gave the value of his own experience in this book but he has covered the literature fairly well in order that one may be able to have a comprehensive idea of what other men are doing in the examination of various parts. This book affords one a comprehensive outline in discussion of the entire roentgenographic technique and should be of great value to anyone doing this type of work. The publisher is to be congratulated on the illustrations and the print.

E. P.

THE DIETARY OF HEALTH AND DISEASE. By GERTRUDE I. THOMAS. Pp. 276; 3 illustrations. Second edition. Philadelphia: Lea & Febiger, 1930. Price, \$2.50.

THE purpose of the book is to serve as a basis for the study of diet in health and disease in schools of Nursing and departments of Home Economics. The consideration of food in its relation to the body needs and the processes by which the body makes use of food are treated in a concise yet comprehensive manner so that the background for the study of foods is adequate.

Diet in relation to the treatment of disease is recognized by the author and the information is up to date, special emphasis being placed on the influence of pregnancy on the teeth, recent developments in diabetic feeding, ketogenic diets and liver therapy for anemia.

The outline for the laboratory course in practical dietetics and suggestions to instructors are of value.

Classification of hospital diets and methods of calculating the caloric value of diets are scientifically treated.

An adequate textbook for nurses.

F. C.

PRACTICAL HANDBOOK FOR DIABETIC PATIENTS. By ABRAHAM RUDY, M.D. Pp. 180; 15 illustrations. Boston: M. Barrows & Co., 1929. Price, \$2.00.

THIS volume is written for the laity. The author devotes several chapters to a description of diabetes, its complications and treatment, emphasizing particularly those facts that the patient should know. The greater portion of the book is devoted to diets, recipes and food values. There are 180 recipes, many of which are from numerous nationalities, so modified that they may be taken by diabetic patients. Apparently the author had in mind particularly the care of the Jewish and other immigrants. These recipes are indexed at the end of the book. The Reviewer feels that the author has presented a book that should be of unusual value to the physician, dietitian and patient.

L. J.

THE TREATMENT OF VARICOSE VEINS. By T. HENRY TREVES-BARBER, M.D., B.Sc. Pp. 120; 11 illustrations.

THE author presents the subject matter in great detail, emphasizing the detail with repetition. He is apparently very well informed on all phases of the condition, but makes no reference to experimental or statistical proofs of his statements and theories. The description of the technique of treatment is comprehensive, but leaves some doubt how to proceed after the first injection.

The injection treatment does not remove the pathology and introduces a chemical irritant which will always produce inflammation. Such treatment is far more out of date than so-called old-fashioned operative method which removes the pathology.

E. E.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. VOL. V. The Pathogenic Streptococci, Their Rôle in Human and Animal Disease, Continued. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), and ROBERT THOMSON, M.B., CH.B. (EDIN.). Pp. 392; 46 plates. Baltimore: The Williams & Wilkins Company, 1929.

VOLUME V of these Annals includes three monographs on the pathogenic streptococci as followed:

VIII. The Rôle of the Streptococci in Oral and Dental Sepsis.

IX. The Rôle of the Streptococci in Tonsillitis and Pharyngitis.

X. The Rôle of the Streptococci in Puerperal Sepsis and Septic Abortion.

These three monographs contain over 1100 references to literature and they are illustrated with 46 full-page plates of photographs of colonies and stained smears of streptococci. The photographs show rather conclusively that the appearance of the colonies on Crowe's medium is one of the most important means we have of differentiating between the large numbers of varieties of streptococci.

This volume, along with Volumes III and IV, is very thoroughly indexed. With Volumes VI and VII (to be published) they will represent an encyclopedia of information on the streptococci and the part they play in human and animal diseases. They cannot fail to be of great service to the future research worker in that they will present the present state of human knowledge on the subject, and they will, therefore, form the basis of further researches and advances for years to come. Those annals impress upon us very emphatically that the streptococcus group is very much larger and more complicated than was ever imagined, and all future researches on this group will require to be carried with much more precision and care than they have been done in the past. W. K.

DIE MEDIZIN DER GEGENWART IN SELBSTDARSTELLUNGEN. Pp. 219. Leipzig: Felix Meiner, 1929. Price, 8.50 Mk.

SEVEN years ago the Leipzig publishing house of Felix Meiner began the publication of small volumes, each containing several autobiographies of men prominent in their line of work. This has now reached the point that in eight fields of human endeavor 30 volumes have been published, including 197 (mostly German) contributors. Though in many cases the most prominent are noticeable by their absence, nevertheless such a project must constitute a source of reference of great value and increasingly so as the series progresses. Following a portrait and short description of the author's birth, education and previous record, the major space is devoted to his scientific aims and achievements that not only give insight into his own personality but also into the thought of the period and specialty. E. K.

PETTIBONE'S PHYSIOLOGICAL CHEMISTRY. By J. F. McCLENDON, PH.D. Fourth edition. Pp. 368; 17 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, \$3.75.

THIS revision of a textbook of Physiological Chemistry which has already been in use a number of years will no doubt meet the approval of those desiring a text which presupposes only a moderate amount of chemical training. The book covers the field of phy-

siological chemistry in adequate fashion although comparatively little space is devoted to fundamental chemical considerations, thus making it much too brief to be used as the sole source of information in a medical school course in physiological chemistry. This is particularly to be noted in the chapters on proteins and carbohydrates where very little attention is paid to even the composition of amino acids and simple sugars. More modern physical methods such as hydrogen-ion determinations find little or no mention in the experimental part of the book. The experiments are otherwise adequate.

J. A.

JAMES MACKENZIE INSTITUTE FOR CLINICAL RESEARCH. GASTRO-INTESTINAL DISEASES. Edited by DAVID WATERSTON, M.A., M.D., F.R.C.S. (EDIN.). Pp. 278; 13 illustrations. New York: Oxford University Press, American Branch, 1929. Price, \$3.25.

THIS publication differs from the previous ones of the James MacKenzie Institute for Clinical Research in that it is not a report of work done there, but a presentation of a series of eleven lectures delivered at St. Andrew's by prominent British physicians and surgeons, all but one from elsewhere. The subjects touch upon the physiology, the pathology and the clinical aspects of gastrointestinal disease. Several statistical reports are included but the number of cases referred to are small. Few if any new data are included, but the accepted British viewpoint about many interesting clinical problems is clearly and entertainingly presented.

T. M.

THE VOLUME OF THE BLOOD AND PLASMA. By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D. Pp. 219; 17 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$3.00.

IN observations on the cellular concentration of the blood, both in clinical medicine and experimental conditions, and on possibly related disturbances in other organs, it is obvious that accurate knowledge of the total blood volume would be highly desirable. This booklet presents the results of the considerable experience of the authors with a dye method which they feel is nontoxic, reliable and has furnished valuable information not only in such conditions as plethora and anemia, but in the relation of blood volume to hypertension, cardiac hypertrophy, etc. Criticisms of the limitations of this and other methods are frankly discussed and details for the proper performance of the test given. We are inclined to agree that the dye method is the best available and may furnish valuable data, but also believe that it unavoidably leaves a number of factors uncontrolled.

E. K.

MANUAL OF DETERMINATIVE BACTERIOLOGY. By DAVID H. BERGEY. Third Edition. Pp. 589. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.

THE elaborate system of classification of the bacteria into families, tribes and genera by a committee on characterization and classification of the Society of American Bacteriologists has made it very desirable to be able to place in the hands of students a more detailed key for the identification of species than any that was available up to a decade ago. This need was in a measure supplied by the first edition of Bergey's Manual in 1923 and is more adequately supplied by the third edition (1930).

More than 200 additional organisms are included in the revision. Two new tribes of soil bacteria have been recognized, each containing a single species. Genus *Eberthella* has been divided by separating the dysentery group from the typhoid group, the former group being placed in the genus *Shigella* while the latter group is retained as genus *Eberthella*. Four additional genera have been recognized in family *Mycobacteriaceæ*, each genus representing characteristic groups of soil bacteria.

The greater number of newly-described bacteria fall in genera *Flavobacterium*, *Pseudomonas*, *Phytomonas*, *Lactobacillus* and *Bacillus*. These additions have necessitated the reconstruction of the keys for these genera. Another change in the Manual is an attempt to arrange the genera of tribe *Bacteriæ* in a way which appears to be more logical. A new key for this tribe as well as the transposing of the locations of the genera in the tribe is presented.

The manual should stimulate efforts to perfect the classification of bacteria as well as prove a valuable aid to the student of bacteriology.

W. K.

BOOKS RECEIVED.

NEW BOOKS.

Plant Biology. By H. GODWIN, M.A., PH.D. Pp. 265; 67 illustrations. Cambridge: University Press, 1930. Price, 8s. 6d.

*The Harvey Lectures, Series 24, 1928-1929.** Pp. 216; 36 illustrations. Baltimore: The Williams & Wilkins Company, 1930.

The Surgical Clinics of North America, Vol. X, No. I, February, 1930, Mayo Clinic Number. Pp. 174; 82 illustrations. Philadelphia: W. B. Saunders Company, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

- The Volume of the Blood and Plasma.*† By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D. Pp. 219; 17 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, \$3.00.
- Progressive Medicine, Vol. I, March, 1930.* Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 328; 23 illustrations. Philadelphia: Lea & Febiger, 1930.
- The Growth of the Mind.* By SIR ROBERT ARMSTRONG-JONES, C.B.E., M.D., D.Sc., F.R.C.P., D.L. Pp. 29; 13 illustrations. Edinburgh: Oliver & Boyd, 1929. Price, Sixpence.
- The Bacteriophage and Its Clinical Applications.** By F. D'HERELLE, Professor of Bacteriology. Pp. 254. Springfield, Ill: Charles C. Thomas, 1930. Price, \$4.00.
- Surgical Diagnosis, Vol. I.** Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 919; 508 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of 3 volumes.
- Surgical Diagnosis, Vol. II.** Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 871; 834 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of 3 volumes.
- Tonsil Surgery.** By ROBERT H. FOWLER, M.D. Pp. 288; 103 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$10.00.
- Peptic Ulcer.** By JACOB BUCKSTEIN, M.D. Vol. X of *Annals of Roentgenology*. Edited by James T. Case, M.D. Pp. 337; 287 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$12.00.
- Cours de Chimie Biologique, Vol. II, Partie Speciale.* By PIERRE THOMAS. Pp. 393; 12 illustrations. Paris: University Press of France, 1929. Price, 60 francs.
- A Syllabus of Lectures on Obstetrics for Nurses.* Prepared by a Committee appointed by the American Gynecological Society. Pp. 38. Copies may be obtained from the Chairman of the Committee, 23 E. 93d St., New York City. Price, 50 cents.

NEW EDITIONS.

- A Textbook of Psychiatry.* By D. K. HENDERSON, M.D. (EDIN.), F.R.F.P.S. (GLAS.), and R. D. GILLESPIE, M.D. (GLAS.), M.R.C.P., D.P.M. (LOND.). Pp. 526. Second edition. New York: Oxford University Press, 1930. Price, \$5.50.
- Practical Psychology and Psychiatry.* By C. B. BURR, M.D. Pp. 378. Sixth edition. Philadelphia: F. A. Davis Company, 1930. Price, \$2.75.
- Medical Treatment of Disease.* By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P. Pp. 516. Third edition. Canada: The University of Toronto Press, 1930. Price, \$4.00.
- Applied Physiology.* By SAMSON WRIGHT, M.D., M.R.C.P. Pp. 552; 128 illustrations. Third edition. New York: Oxford University Press, 1929. Price, \$5.50.

* Reviews of titles followed by an asterisk will appear in a later number.

† See p. 706 this number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases.—Without enumerating all of the statistical findings in this study by TURNER (*Bull. Johns Hopkins Hosp.*, 1930, 46, 159), it is of interest to note in these 10,000 ambulatory patients a few of the following facts: Clinically recognizable syphilitic affections of the cardiovascular system occurred in 10 per cent of all the cases and the proportion of males to females and negroes to whites was approximately as 2 is to 1. Uncomplicated aortitis with or without aneurysm occurred much more frequently in males than in females and in negroes than in whites. Aortic regurgitation is more than twice as common in males as in females and is just about as common in whites as in the negro. Syphilitic angina pectoris was rare and was seen more frequently in whites than in negroes. Central nervous system syphilis was observed in late syphilis in 39.3 per cent of white males and only 15.9 per cent of colored males. The ratio was approximately the same among the females of the two races, but the nervous system involvement was only about one-half as frequent as with the males. General paresis was very much more frequent in the whites than in the blacks and the same thing applies to tabes dorsalis. Cerebral vascular syphilis was more common in the negro than in the white. Syphilitic stricture of the rectum was confined almost entirely to colored females. Pulmonary tuberculosis among the negro syphilitics was decidedly less than in the general negro population and diabetes was no more frequent among the syphilitics than among the nonsyphilitics.

Studies on the Effect of Nitroglycerin, Amyl Nitrite and Acetylcholine on Hypertension.—ZEISS and BRAMS (*Am. Heart J.*, 1930, 5, 300) write that the medical treatment of hypertension is frequently unsatisfactory

and often most disappointing, possibly due to the fact of the traditional belief that nitrites reduce blood pressure regardless of the cause. They decided to reinvestigate the influence of these drugs on account of the very many contradictory reports that now occur in the literature. They summarize their investigations as follows: Nitroglycerin produces a fall in blood pressure in normal controls, but inconstantly in patients with hypertension. Amyl nitrite causes a fall in both controls and hypertensive cases. A secondary rise above the previous level of the pressure occurs in a certain number of cases of patients who receive amyl nitrite or nitroglycerin. Amyl nitrite exerted its effects more markedly and lasted almost as long as did the effects obtained by nitroglycerin, but disagreeable symptoms frequently followed the use of this drug. Acetylcholine was found to be inert in both the controls and the cases of hypertension, a finding quite different from the claims made for this drug in literature.

Brucella Abortus Infection in Man.—The increasingly large number of Brucella infections reported throughout the country have focused interest on the Brucella group of organisms. There has been a tendency among clinicians to consider various types of organisms belonging to the group of Brucella (Alkaligenes) as being capable of producing very much the same clinical symptoms in all cases. GIORDANO and SENSENICH (*J. Lab. and Clin. Med.*, 1930, 15, 421) have analyzed a series of 35 cases and have come to the conclusion that Brucella abortus infection in man runs a clinical course somewhat at variance to that of Brucella melitensis infection. In this series of 35 cases reported by the authors they give the following data: There were 20 men and 15 women in the group and the preponderance of infection is in the second, third and fourth decades. Occupation, they say, is an etiologic factor only in so far as it provides opportunity for infection, such as those engaged in the handling of infected animals. Consequently there is a very much greater incidence among farmers and farmers' wives than in any other occupation. The disease is commoner in rural communities because raw milk is more generally used. This is probably an important mode of infection, as judged by reports from others, of the disease occurring in individuals who have ingested milk from abortus-infested cows. The onset is usually insidious, with fatigue, low fever, headache and joint pains. Often there is involvement of the upper respiratory tract. The disease may be characterized by either an acute or chronic course, the latter corresponding closely to the type of disease observed in an individual who has undulant fever of the melitensis type. In Brucella abortus infection acute types are more frequent than the chronic and this the authors consider to be an important differential point between the two forms of Brucella infection. They divide the cases into several groups, such as the septic, the arthritic, neurologic, visceral and glandular, according to the predominance of the symptoms. Fever is the most constantly present symptom and, of course, is invariably present. There is some tendency to undulation when the temperature charts are studied, but the period of undulation is shorter than in Brucella melitensis infection. The whole febrile course is shorter. Arthralgia, arthritis and neuritis are other rela-

tively common symptoms which deserve to be accentuated. The blood count shows that the white cells are decreased in number, as a rule, so that late in the course of the disease the count varies from 6000 to 10,000. Only two blood cultures were positive in twenty attempts. The agglutination reaction is the most valuable clinical laboratory evidence of the disease. A positive reaction occurs early and the agglutinin titer is high. There seems to be no relationship between the titer of the agglutinins and the severity of the disease. Rest in bed seems to be the important symptomatic treatment.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Distribution of Blood in Shock.—BLALOCK and BRADBURN (*Arch. Surg.*, 1930, 20, 26) claim that the oxygen content of blood from the right side of the heart, portal vein, femoral vein, external jugular vein, the renal vein and the femoral artery has been determined in dogs to which barbitol had been given for varying intervals of time. Similar studies were made after a low blood pressure had been produced by hemorrhage, the injection of histamin, trauma to the intestinal tract, trauma to the cerebrum and trauma to one of the posterior extremities. In the control experiments, the oxygen content of blood from the right side of the heart and that of blood from the portal vein were approximately the same; that of blood from the femoral vein was usually lower and that of blood from the external jugular vein slightly higher. The oxygen content of blood from the renal vein was usually definitely higher than that of the mixed venous blood. Approximately the same relationship existed between the values of the oxygen content of blood from the various sites after a low blood pressure had been produced by hemorrhage, by histamin and by trauma to the brain. The oxygen content of blood from the portal vein was much higher relatively after trauma to the intestines, while that of blood from the extremities and head was low. The oxygen content of blood from the femoral vein of a traumatized leg was high, while that of blood from the opposite extremity and head was low. The oxygen content of blood from the renal vein was relatively high in all the experiments. These observations suggest a local accumulation of blood at the site of trauma to a large area, such as the intestinal tract or an extremity, and are evidence against the action of a histamin-like substance that produces a general bodily effect.

Primary Intramuscular Hemangiomas of Striated Muscle.—DAVIS and KITLOWSKI (*Arch. Surg.*, 1930, 20, 39) say that primary angiomas of striated muscles are no longer rare tumors, as is indicated by the 212 cases here collected. It is a slow-growing tumor, congenital in origin,

with trauma playing a rôle more in its growth than in its origin. It occurs about equally in both sexes. The age of onset is before the twenty-first year in the great majority of cases, the largest number occurring before the eleventh year. The tumor may occur in any striated muscle. The lower extremities are most commonly affected and the upper extremities are next. The larger and more powerful muscles are involved most frequently. The size of these tumors range from that of a nut to that of a small pumpkin. The chief symptoms are pain, swelling and functional impairment. The tumor may be compressible and change in size with changes of posture. It is usually soft, but may be hard, smooth or lobulated, movable or fixed, circumscribed or diffuse. The diagnosis is difficult. Aspiration of normal blood is a valuable aid. The existence of simple angiomas is questioned and the cavernous type is considered the only one found in striated muscle. On section it has the characteristic appearance of a blood-filled sponge. Microscopically the typical picture is that of blood-filled spaces containing normal blood, which either are lined by endothelium or have walls composed of fibrous connective tissue. The muscle fibers show degeneration ranging from hyaline to fat replacement. The only treatment of value is excision, while the prognosis is excellent.

Primary Carcinoma of the Ureter.—ROUSSELOT and LAMON (*Surg., Gynec., and Obst.*, 1930, 50, 17) declares that primary carcinoma of the ureter is a rare lesion. Previous to the case reported here only 49 cases have been recorded in the literature. The most common type of carcinoma is the so-called papillary epithelioma. Less frequent is the squamous-cell tumor, of which the present case is an example. Ureteral carcinomata metastasize widely, traveling by venous and lymphatic channels. Renal calculi are occasionally associated with this neoplasm. Many authors believe that stones, by their irritative action, are an important causative factor in the production of epithelial tumors of the genitourinary tract. In the cases here reviewed, no frequent association of stones and tumor could be discovered. The two most constant symptoms of this disease are pain and hematuria. The condition is rarely diagnosed before operation or necropsy. Roentgen ray and cystoscopic examinations are the most important diagnostic aids. Removal of the affected ureter and kidney is the treatment of choice. The course of the disease following any form of treatment has been discouraging. In only one recorded case was the patient symptom-free two and a half years after being first observed.

Some Surgical Problems in Jaundiced Patients.—SMITH (*Am. J. Surg.*, 1929, 7, 799) claim that the fear of operating unnecessarily on a patient in the cancer age, with possible catarrhal jaundice, need not delay surgical intervention after careful study of the case. In obstructive jaundice, due to malignancy in this series, pain, occasionally severe, was found in more than half the cases. It was relatively more common in duct than pancreatic carcinoma. Silent stone in cases of jaundice thought to be due to malignant disease is disappointingly uncommon, but is a reason for exploration. Biliary intestinal anastomosis in malignant obstruction of the ducts is a palliative measure, which seems worth while. An occasional case thought at operation to be carcinoma of the pancreas, will turn out to be pancreatitis.

THERAPEUTICS

UNDER THE CHARGE OF

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Some Pharmacologic Aspects of Tribromethylalcohol ("Avertin").—In discussing the relative value of the rectal administration of anesthetics, PARSONS (*Brit. Med. J.*, 1929, p. 709) claims that the advantage of this channel of administration is that it is more comfortable for the patient, it does not require an anesthetist and it is specially convenient for operations about the head and neck. The disadvantages are the risk of irritation to the mucosa, the difficulty of maintaining a constant concentration in the tissues and the impossibility of controlling its action after administration. Avertin is a trade name for tribromethylalcohol, which has received widespread use as an anesthetic in Europe. On the basis of pharmacologic observations, Parsons claims that special care must be exercised in the preparation of solutions of avertin for anesthesia. Heat over 50° C., light and air are apt to produce decomposition products irritant to the rectal mucosa. Tribromethylalcohol in doses just sufficient to induce deep anesthesia exerts no appreciable effect upon the cardiovascular system. When administered in larger amount it slows the cardiac rate and weakens the force of the beat. Under experimental conditions the coronary vessels dilate and the blood pressure falls. Tribromethylalcohol anesthesia is accompanied by marked slowing of respiration, which is due at least partly to diminution of voluntary movements and to absence of reflex activity from the respiratory tract. Certain peculiarities of the respiration may be observed when the anesthesia is deep. Respiratory paralysis is the cause of death from toxic doses. Tribromethylalcohol is excreted in the urine over a period of several days; but more than 50 per cent is excreted in the first twenty-four hours. The chemical nature of the elimination cannot be determined at present. It is suggestive that the elimination occurs in the form of an organic compound of bromin.

The Clinical Use of Tribromethylalcohol ("Avertin") Narcosis.—EDWARDS (*Brit. Med. J.*, 1929, p. 713) states that the variations in depth of anesthesia produced by similar doses of avertin on different patients is so great that one cannot set out definitely to produce anesthesia solely by this method. Once a patient is narcotized with avertin, only a very small quantity of inhalation anesthetic is required to com-

plete the anesthesia. The falling asleep is gradual and peaceful. Even if the narcosis has been slight, there will be no memory of anything from the time of injection. The events of the next twenty-four or thirty-six hours will not be remembered with any clearness. It is of particular value in highly nervous patients, with cases of Graves' disease. The drug is contraindicated in patients with inflammatory and ulcerated conditions of the rectum and colon; in cases with severe renal and hepatic lesions, acidosis, advanced cachexia and serious blood diseases. There is a fall of 10 to 30 mm. of mercury in the blood pressure during this narcosis. The breathing is shallow and the rate normal or slightly slow. Variable degrees of cyanosis may be present. It takes twenty to thirty minutes to reach completion of the anesthesia. The preliminary measures are an enema the night before operation, repeated the next morning if necessary. One-tenth gram per kilo of body weight is a safe dose. Untoward reactions almost always are due to overlarge doses. The weighed powder of tribromethylalcohol may be dissolved slowly in water at 38° C. It is provided in a concentrated solution with amylene hydrate—1 gram in 1 cc. The approximate amount of the solution is measured out and distilled water to make 2.5 to 3 per cent solution is added at 38° C. The mixture is shaken until clear solution results. *The temperature must never exceed 40° C.* Just before administration a drop of 1 in 1000 Congo red solution is added to 5 cc. of the dilute solution. The color of the solution should remain bright orange red. The solution is injected into the rectum slowly through a catheter and funnel. The injection should take three to four minutes. It is best to give the rectal injection thirty minutes before the expected start of the operation. Ether, chloroform or local anesthetics are used to supplement tribromethylalcohol. Combined with volatile or local anesthetics, avertin is a satisfactory anesthetic agent. It should be remembered, however, that it is not controllable and cannot safely be used as the sole anesthetic agent. It requires an experienced anesthetist to control the superimposed anesthesia. In certain cases and types of patients avertin is of great value. As a routine agent it is hardly practicable.

Use of the Duodenal Tube in the Treatment of Infestation by *Tænia*.

—MARGULIS (*München. med. Wchschr.*, 1929, 76, 1510) strongly recommends the administration of tæniacids by means of the duodenal tube on the basis of an extensive experience of the past two years. Although this method of administration is exceedingly satisfactory in adults, it is exceptionally so in children. Not only does the method seem to diminish the danger of intoxication on account of the more rapid action and elimination of the anthelmintic agents employed, but, owing to this fact, larger doses of these drugs may be given with safety as absorption is diminished. As a result, the method yields a higher proportion of effective cures than does oral administration. The usual preliminary period of starvation and cleaning out of the gastrointestinal tract by laxatives precedes the administration by duodenal tube just as it does the oral administration or vermifuges.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Incidence of Sinusitis in Asthmatic Children.—CHOBOT (*Am. J. Dis. Child.*, 1930, 39, 257) states that the incidence of sinus infection in asthmatic and also in normal children is much higher than has heretofore been believed. In his series of 100 asthmatic children, 60 were boys and 40 were girls. Fourteen had their first attack in the first year of life and 19 in the second year. These figures compare closely with reports of other observers. Fifteen of these patients had negative skin reactions. The incidence of the age of onset is parallel to that in hypersensitive patients. Fifteen per cent of the sensitive patients had their first attack in the first year and 23 per cent in the second year. The 15 negative cases in this series were studied and a positive family history was obtained in 5 children. Forty-one of the entire series both sensitive and nonsensitive had sinus infections as demonstrated by Roentgen ray examinations. Chobot recommends conservative treatment but he feels that puncture and irrigation should be performed when conservative measures have failed.

Citric Acid Milk in Infant Feeding.—GONCE and TEMPLETON (*Am. J. Dis. Child.*, 1930, 39, 265) made a comprehensive study of the feeding of citric acid milk to infants. One of their chief claims for its use is that it is easy to prepare. They found that the hydrogen-ion concentration of the gastric contents at the height of digestion in infants who were fed on whole citric acid milk averaged 3.72 in the normal infants, 4.15 in the abnormal infant. The gastric curves at the height of digestion on this type of milk were uniformly small. The average individual curves being less than 1 mm. in diameter and the largest being less than 3 mm. in diameter. Infants seemed to like citric acid milk and in itself it never caused persistent vomiting. It was found that the infant fed on whole citric acid milk both in the hospital and at home gained weight better than with the normal expectancy. The stools of these infants were of a smooth pasty or firm consistency and were somewhat more frequent in number than infants fed on simple milk dilutions. The citric acid in the amount of 4 gm. to a quart of milk did not show any toxic action on the kidneys. The authors feel that since citric acid milk appears to equal lactic acid milk in the beneficial results and because of its constant acceptability and ease of preparation that it is specially fit for use in rural districts and in all homes in which ice is not available.

The Etiology of Infantile Spasmophilia.—GERSTENBERGER, HARTMANN, RUSSEL and WILDER (*J. Am. Med. Assn.*, 1930, 94, 523) present additional data in substantiation of the theory advanced by them in a previous report. This theory is that there are three factors essential

in the development of infantile spasmophilia and these factors are, rickets, exposure of the rachitic infant to the influence of the anti-rachitic factor in one form or another sufficient to produce partial healing and interruption of the exposure or inadequacy of the exposure. They report the appearance of typical spasmophilia following interrupted therapy in two rachitic infants who were exposed to sunlight and in another rachitic infant who received inadequate therapy in the form of human milk possessing some antirachitic power. The two infants who were exposed daily at noon to the sun for an hour as it passed through glass that was more permeable to ultraviolet rays than is ordinary window glass. The other infant developed spasmophilia after and while being fed milk from a wet-nurse whose arms, face and neck were exposed daily to the summer sun for forty-five minutes. This milk had antirachitic power but not in a marked degree and in this rachitic infant furnished an inadequate intake of the antirachitic factor. Another child developed mild symptoms of spasmophilia after a single erythema-producing exposure to the quartz light. The authors define infantile spasmophilia as a symptom complex occurring principally in spring and fall peaks and characterized by a higher excitability of the nervous system.

Poliomyelitis.—RILEY (*J. Am. Med. Assn.*, 1930, 94, 550) emphasizes the importance of the early diagnosis before paralysis appears. He feels that when a patient, especially a child, appears prostrated out of proportion to the temperature, with flushed face, anxious expression, mild injection of the throat, rapid pulse, a coarse tremor or movement, the head tilted on the neck, stiffness of the spine and pain on anterior flexion, and an increase in the cellular and globulin contents of the spinal fluid, the diagnosis of poliomyelitis is definite and convalescent serum should be administered. No untoward results from the use of convalescent serum should be feared and even if there is an error of diagnosis no harm will follow from its administration. Early and repeated spinal drainage and the use of convalescent serum are most important in the preparalytic stage of the disease. When it is realized that the pathologic changes of this disease are located in the central nervous system it is obvious that in order to prevent as much as possible the paralysis and to obtain the greatest functional activity. Prolonged rest in the recumbent posture is necessary. As a result of this method of handling the number of patients with poliomyelitis recovering without appreciable paralysis during the 1928 epidemic in Maryland and in recent epidemics elsewhere is most encouraging. Under proper conditions the good recovery was found between 70 and 80 per cent of the cases as compared with 20 per cent in cases receiving less intensive treatment. He feels that under appropriate treatment 90 per cent of the deformities which have followed epidemics may be eliminated and deformities as an after result of the disease should entirely disappear. This statement is based upon the early treatment of the disease as an absolute necessity. Along with the use of human serum, early hospitalization and the guidance of an orthopedic surgeon are additional factors which produce low mortality rate, low average of total paralysis, a striking reduction of paralysis of severe grade and complete prevention of deformities.

Chorea.—EPSTEIN (*Arch. Ped.*, 1930, 47, 119) claims that chorea in children is a cerebrospinal and an autonomic functional neurosis and that it requires some infection, physiologic distress or psychologic insult to convert it into a disease process. The signs and symptoms of chorea are the result of the primary neurosis and secondary process may be pathologic, physiologic or emotional. Where a choreic child may show evidence of pathologic, physiologic and psychologic abnormalities, one of these usually predominates and suggests the proper group diagnosis. Chorea frequently leaves in its wake a damaged heart or an impaired neuropsychic system. Both the choreic process and the secondary disorder contribute to the cardiac or nervous breakdown and treatment should be prophylactic as well as curative. Every effort should be made to keep nervous and emotional children in good physical and mental health. Careful guidance in the home and school life is necessary in order to avoid an overtax. During the acute stage good food, complete rest, hygienic care, salicylates, bromides or hypnotics will be of help in bringing about recovery. Recurrences of chorea must be prevented by proper and constant attention to the well-being of the child, especially as regards the hours of work, rest and play.

Measles Prophylaxis with Serum of Adults Who Had Measles in Childhood.—VAN CLEVE (*Arch. Ped.*, 1930, 47, 124) believes that immune measles goat serum or antistreptococcus measles antitoxin will be the best form of serum to use because it will be easily available and will be standardized. He feels that convalescent serum is equally as good but not generally practical and there is some danger of transmitting tuberculosis or lues. Serum of adults who had measles in childhood is not as efficacious, but where the others are not to be had it will answer. It will protect the young and malnourished and modify the disease in the older children and lessen the danger of complications in children under four years. The undernourished, the rachitic, the tuberculous and delicate are much safer with full protection with a dosage sufficiently large to assure this. In older children and adults it would seem better to give a dosage sufficient to modify the disease as it had been shown that serum only protects from four to six years while the modified cases have a lasting immunity that is indefinite.

DERMATOLOGY AND SYPHILIS

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Syphilitic Disease of the Pulmonary Arteries.—HARE and ROSS (*The Lancet*, 1929, ii, 806). The authors report a case of pulmonary arteritis together with a review of 23 previously published cases. Of the

24 cases, 16 had a definite syphilitic basis, 2 were syphilitic but with nonsyphilitic histology, 1 followed typhus and the remaining 5 were primary. Age and history of the patient give the sole clue to the possible luetic origin in those affected. To quote from the author's summary: It is found that syphilis is by far the most important etiologic factor in older patients. Primary noninflammatory sclerosis of unknown etiology is found in younger patients. In the syphilitic cases the lesions in the intrapulmonary arteries take the form of an obliterative arteritis, usually most severe in the smaller branches and arterioles. This condition leads to a raised blood pressure in the lesser circuit. Dilatation and hypertrophy of the main pulmonary artery follows with atheroma of the right and left pulmonary arteries and larger branches, whether the latter show inflammatory lesions or not. The right side of the heart becomes greatly dilated and hypertrophied. Clinically the cases are characterized by dyspnea, cyanosis and hemoptysis, and in the later stages by progressive congestive heart failure with a regular pulse. Syphilitic arteritis of the pulmonary arteries, while admittedly rare, is worthy of notice, since by early diagnosis antisiphilitic treatment might afford some hope of amelioration of the symptoms.

Arsphenamin Sensitization Tests Including a Report of Arsenical Dermatitis Due to the Arsenobenzol Radical of Bismarsen (Bismuth Arsphenamin Sulphonat).—SCHOCH (*Am. J. Syph.*, 1930, 14, 75). The desirability of determining patients' cutaneous tolerance to the arsphenamins prior to the administration of the drug prompted the author to attempt an evaluation of the different methods of testing for cutaneous hypersensitiveness to the arsphenamin group. The various methods previously employed are discussed, and the functional skin test of Jadassohn (eczema test of Bloch) is selected as the most promising at the present time. It was found that strongly positive reactions were obtained with this method in all patients with known cutaneous hypersensitiveness to the arsphenamins (four), and negative in a series of 96 persons who showed no cutaneous intolerance to the drug. A case of generalized subacute dermatitis with erosive stomatitis following the administration of bismarsen is included. Evidence is given that the patient's hypersensitiveness was acquired, that it was specific for the arsenobenzols, and that it was not due to the bismuth content of bismarsen. The author believes that this is the first case of extensive dermatitis due to the arsenobenzol radical of bismarsen reported in the literature. Passive transference tests by the Prausnitz-Kustner method and by Perutz's modification of the Konigstein-Urbach method gave negative results. A résumé of the literature on arsphenamin hypersensitiveness is included, with special reference to cutaneous methods of testing and passive transference. The author's findings are interpreted in the light of the recent literature on the subject. Schoch concludes that in certain reported cases the interpretation of positive reactions as indicative of successful passive transference were specious. He furthermore points out that in all probability active sensitization was brought about by the introduction (intradermally) of minute amounts of the antigen, instead of the specific antibodies which would produce passive sensitization.

The Kline Slide Precipitation Test for Syphilis.—MILLER (*Am. J. Syph.*, 1929, 13, 583). The author emphasizes that in the evaluation of new tests against older and more standard procedures, clinical findings should determine the basis of the comparison. The author reports on 1813 tests done on 1058 patients and divided between proved cases of syphilis and nonsyphilitic cases. The Kline test was compared with the Kolmer Wassermann and the Kahn precipitation tests. Miller found the Kline microscopic slide precipitation test technically simple and requiring less time and apparatus than either the Kolmer Wassermann or the Kahn tests. In addition the reaction is easier to read than that of the Kahn test and is at least as easy to read as the Kolmer Wassermann reaction. The Kline slide test may be done with anti-complementary and slightly hemolyzed blood. The number of positive reactions given by the Kline slide test was greater than the positives produced in the two comparing tests with the exception that in cases of cutaneous syphilis and neurosyphilis the Kolmer Wassermann gave the higher percentage of positives. The Kline and Kolmer tests appeared equal in the recognition of cardiovascular syphilis. The Kline test showed an earlier positive reaction in primary syphilis than either the Kolmer Wassermann or the Kahn test, and it showed a tendency to slower reversal to negative in cases of primary syphilis under treatment. The Kline slide test, however, gave a higher percentage of false positives than either the Kolmer Wassermann or the Kahn tests.

GYNECOLOGY AND OBSTETRICS

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Irradiation of Ovarian Cancer.—Perhaps the most carefully checked results of irradiation of the female pelvic organs are those obtained at Radiumhemmet in Stockholm so that when an opinion issues from such a source it is of value. In a report emanating from this institution, HEYMAN (*Surg., Gynec. and Obst.*, 1930, 50, 173) recalls that in the gynecological literature the five-year cure by operation alone in radically operable cases of cancer of the ovaries is generally estimated to be about 30 per cent, somewhat higher for unilateral and considerably lower for bilateral tumors. Judging from his results a permanent cure is more often obtained from radical operations when combined with postoperative irradiation since in a series of 32 cases he has had 65.6 per cent of five-year cures. In cases in which it has been impossible to perform a radical operation because of metastases, but in which it was possible to remove the ovarian tumors, remarkable results have often

been obtained by radiologic treatment. In a series of 30 such cases treated at Radiumhemmet there are quite a number of patients who for several years have been kept free from symptoms and able to work, there being 7 who were under observation for over five years. In completely inoperable cases the radiologic treatment is of an exacting nature, but can, if correctly carried out, bring with it a remarkable reduction of the tumor and a marked temporary improvement in the general health of the patient. In some cases the patient can be kept free from discomfort for one or two years. In recent years he has performed a re-laparotomy in those cases in which the tumors have shrunk and become mobile under radiologic treatment. In 3 out of 5 such cases the operation was easily performed. He is of the opinion that no permanent results can be obtained in the treatment of cancer of the ovaries without resort to surgical intervention. On the other hand, it is undoubtedly true that an intimate coördination of radiologic and surgical treatment can improve the results considerably. The removal of the ovarian tumors should always be tried, if the risk involved is not too great. If the risk is too great, then it is better to trust to radiologic treatment. In the surgical treatment he advises not to remove the uterus but to retain it so that it may be used as a means of applying the radium in after-treatment, thus enabling the radium container to be centrally placed in relation to the original site of pathologic change. This should be done without delay after operation.

Treatment of Gonorrhea with Living Organisms.—On a previous occasion we have called attention to the method of treating gonorrhea of the female genital organs by means of the subcutaneous injection of living gonococci. LOESER (*Zentralbl. f. Gynec.*, 1930, 54, 163) who is the originator of the method is able to report the results he has obtained following 1500 such injections, none of which gave any dangerous complications. Within two to four weeks, during which time 1 to 3 such injections are given, a cure was obtained in 60 to 70 per cent of the cases of gonorrhea of the cervix, adnexa and joints. An even higher rate of cure can be expected if the cervical canal is treated with a silver preparation every other day between the injections. He has found that the treatment is of value only in the closed type of gonorrhea in the chronic stage, so that no results may be looked for in disease of the urethra and lower genitals. In order to make the cervical canal a closed organ an occlusive cap is worn over the cervix between treatments. The gonococcal culture which is used for the injection should be reasonably fresh as the older the culture, the less potent it becomes; even transplanting it does not retain its value as these organisms rapidly lose their strength when they are outside of the human body. For best results a mixed fresh culture of 3 or 4 strains of gonococci should be used. In order to show that he has no fear of such injections, Loeser states that in the beginning of his work he was the first experimental animal as he injected live gonococci under his own skin. The injection causes a small somewhat painful infiltration at the site of the puncture which is followed by an erythema within twenty-four hours but which disappears entirely within three days. The body temperature rises a degree or so and the patients may complain of a slight headache, but in no case has there been a general blood stream infection following the injection.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Cytologic Examination of the Antrum. Review of Cases to Determine Relationship Between the Cytologic and the Roentgen-ray and Pathologic Observations.—Aware of the potential difficulties in localizing the particular site of involvement in suspected cases of sinusitis, and having previously called attention to the fact that simple lavage of a sinus is untrustworthy as a diagnostic procedure,¹ SEWALL and HUNNICUTT (*Arch. Otolaryngol.*, 1929, 10, 1) again offer evidence to show that cytologic examination of fluid recovered from the antrum is a valuable adjunct to the diagnostic armamentarium of maxillary sinus disease. After outlining the technique and discussing at considerable length the pathologic histology of sinusitis, comparative roentgenographic, cytologic and postoperative microscopic findings of eighty-three examinations on 55 persons are tabulated. All of these 55 patients had chronic nasal discharge; and on each occasion the material recovered from the antrum showed one or more types of leukocytes. Of the entire series, roentgenograms showed the antrum to be clear in 13 per cent. The test water was macroscopically clear in 18 per cent of the cases presenting cytologic evidence of sinus infection, and it contained easily overlooked shreds of white mucus in 54 per cent. The authors have made the interesting observation that the antra showing the least evidence of infection (by their method) have been associated with definite disease of the opposite maxillary sinus. Employing essentially the same methods for collection and study of the aspirated fluid from 25 cases of suspected sphenoiditis, TILLOTSON—"Sphenoiditis. Value of Cytologic Studies in Diagnosis." (*Arch. Otolaryngol.*, 1929, 10, 262)—was able to identify mono- or polymorphonuclear leukocytes in the centrifuged specimens in all save four instances. From his results the author concludes that if one bears in mind the clinical symptoms and utilizes the various physical aids at one's disposal, including cytologic study of the sinus secretion, the diagnosis of sphenoiditis—and its commonly associated condition, posterior ethmoiditis—may be made more easily.

Traumatic Conditions of the Ear in Workers in an Atmosphere of Compressed Air.—In the condition known as caisson sickness or disease, the symptoms referable to the auditory apparatus occupy a prominent position. Outstanding among the aural symptoms may be mentioned varying degrees of impaired hearing, a feeling of fullness in the ear, tinnitus, vertigo and autophony. These clinical manifestations have been ascribed by various observers: (1) to the direct action of the compressed air-producing hyperemic and hemorrhagic states in the middle and internal ears or rupture of the tympanic membranes; or (2)

¹ Vide Retrospect: *AM. JOUR. MED. SCI.*, 1929, 177, 296.

to the liberation of nitrogen bubbles in the cochlear and vestibular apparatus. After reviewing the literature and citing two illustrative cases, VAIL (*Arch. Otolaryngol.*, 1929, 10, 113) reports the results of several experiments on rabbits—so conducted as to simulate working conditions as nearly as possible. Microscopically it was found that in every case the lesion was essentially the same, consisting of a copious hemorrhage into the middle ear and its vestibule. Eustachian tubal blockage did not seem to alter the histologic picture. The structures of the internal ear were not affected to any appreciable degree. The author states that trauma can be inflicted on the middle and internal ears of workers in an atmosphere of compressed air, not only during compression but also during, or after, decompression. In the first group the aural trauma is caused by nonequalization of the pressure within and without the middle ear and transmitted to the internal ear, with resulting stasis and hemorrhage; and the symptoms may be temporary or permanent. In the second group the otitic lesions are due to bubbles of nitrogen-forming emboli or areas of necrosis in the internal ear; and the symptoms usually are permanent. It is suggested that in workers in compressed air, the ears and nasal sinuses should be examined carefully; that persons who have suffered traumatic rupture of the drum-heads should undergo recompression only if symptoms of caisson illness appear; and that a survey must be made to decide whether the percentage of deafness is uniformly high in individuals working under compressed air.

Chondroma of the Larynx.—In view of the fact that only 69 cases have been collected from the literature, laryngeal chondroma is a decidedly uncommon tumor. Nevertheless, it is an important one, as shown by the instructive case reported by CLERF (*Arch. Otolaryngol.*, 1929, 10, 241). In Clerf's patient there had been a history of progressive hoarseness of six months' duration but the only findings consisted of immobility of the left vocal cord and impairment of motility of the right cord. Four and one-half years later, however, a previously unrecognizable cartilaginous tumor had grown to a size sufficient to cause a dyspnea that necessitated tracheotomy and subsequent laryngectomy. A convincing photomicrograph is presented.

Nonsurgical Treatment of Chronic Middle Ear Suppuration, Based Upon Twenty-five Years' Experience.—Following a brief résumé of the various bacteriologic, pathologic and clinical aspects of his subject, BECK (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 1150) says that "up to quite recently,—I have not been very much encouraged in the local treatment of chronic suppuration" (of the tympanic cavity), "but since then, and particularly in the last six months, I feel much encouraged." He refers especially to a method involving capillary suction from the attic region with subsequent insufflation of boracic acid powder containing iodine. Calot's solution also has been used in lieu of the powder, but with less success. The introduction of water into the aural canal is harmful to chronically discharging ears. Local and general contributory pathologic conditions should be properly managed.

RADIOLOGY

RADIOLOGY

UNDER THE CHARGE OF

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Physical Therapy in Infantile Paralysis.—KEY (*Arch. Phys. Therap., X-Ray, Radium*, 1929, 10, 385) insists strongly that no form of physical therapy should be used until the tenderness has entirely disappeared from the paralyzed muscles, and the duration of this period varies from a few weeks to several months. This acute stage is followed by a convalescent stage which lasts two or three years. This stage is characterized by a tendency of the paralyzed muscles to recover their tone and power, and this is the period during which physical therapy is especially beneficial. Protection from stretching and overwork, graded exercises and local heat and massage may be accepted as beneficial, and their relative value is in the order mentioned. Protection from stretching is most important and is accomplished by the application of splints of metal, leather, wood, etc. This support should be maintained until the muscle has regained sufficient power to support the part without damage, or until all hope that it will regain such power is abandoned. Voluntary exercises must take the form of carefully supervised muscle training. They should be as simple as possible in order that they may be performed accurately, and light at the beginning. When the muscle is too weak to move the part against gravity the patient can be placed in water. Swimming pools are an important feature of many institutions. Heat to the paralyzed muscles is usually applied in the form of a simple electric baker, but diathermy or moist heat or some other form of dry heat may be used. There is no evidence that any particular type of heat is best. The heat is followed by gentle massage and this by muscle exercise. Key does not advise the use of electricity in its various forms because he does not believe that it is of practical value and may do more harm than good because it is apt to divert the treatment from muscle training which is of the utmost importance. This objection is true of light therapy and heliotherapy. Ultraviolet light and heliotherapy may be used for their general effect on the patient, but are not to be regarded as agents for the restoration of paralyzed muscles.

X-ray Examination of the Heart in Beriberi.—For some time KEEFER and HSIEH (*Radiology*, 1929, 13, 211) of Peking Union Medical College have been interested in the cardiac changes observed in beriberi. They have found that in all cases of beriberi with cardiac insufficiency the heart was enlarged, and frequently there was considerable enlargement in cases without insufficiency. The enlargement was principally right-

sided, involving both the right auricle and ventricle, and the pulmonary artery was prominent in many cases. There was also enlargement of the superior vena cava. The size and configuration of the heart changed completely following treatment, and it assumed a normal size and shape after a varying length of time. —

Activated Ergosterol in Radiation Sickness.—For the prevention and alleviation of radiation sickness the administration of calcium lactate has proved beneficial. It occurred to SMITH (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 317) that to increase the body calcium the administration of ergosterol might be more efficient, and it was tried in 55 cases. The product used was a solution of ergosterol in peanut oil and was given in doses of 4 to 8 minims, twice or three times daily, beginning preferably twelve to twenty-four hours prior to treatment and discontinuing twelve to twenty-four hours after irradiation. Seventeen patients who had previously been nauseated by irradiation experienced no nausea after taking ergosterol; 29 patients not previously irradiated had no nausea; 10 patients experienced nausea despite the treatment. Marked relief of all symptoms, except possibly diarrhea, is usually effected. Used as a prophylactic ergosterol prevents all symptoms to a marked degree. Many of the patients experience an unusual sense of well-being and an increased appetite. The action is probably effected through the calcium phosphorus metabolism. There is some evidence that the final effect may be brought about through prevention or reduction of hyperirritability of the vagus. The method is apparently applicable both to radium and roentgen treatment. —

Physical Therapy in Thoracic Surgery.—Heliotherapy is used routinely by BETTMAN (*Arch. Phys. Therap., X-ray, Radium*, 1929, 10, 444) during the convalescence of cases of empyema, lung abscess, tuberculosis of the lungs, and bronchiectasis. It is never given until the patient has become afebrile. It is stopped the moment any inflammatory recrudescence occurs. It is started in small doses and gradually increased. It is given for its general tonic effect. In one type of operation, that of cautery lobectomy, it is used for the mild local stimulating effect, granulation of the wound apparently being improved by daily exposures to the quartz lamp. In many unilateral diseases of the lungs and pleura there is a marked tendency to the development of scoliosis. Exercises to overcome deformity should be started as soon as the patient's condition permits. This applies also after plastic operations in empyema and pulmonary tuberculosis. Surgical diathermy is the method of choice for local recurrences following amputation of the breast for cancer, and for tumors of the ribs, chest wall and pleura in which a massive sharp resection and subsequent closure are impossible. For incision of pulmonary tissue the endothermic knife is greatly to be preferred over sharp dissection in that it severs tissue without pressure. The consistency of the lung is such that it is extremely difficult to cut unless it is held taut either by adhesions or by forceps, and so forth. The pressure required, even when a very sharp knife is used, is often sufficient to tear the lung at the point of adhesion or fixation with forceps.

NEUROLOGY AND PSYCHIATRY

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Nervous and Mental Phenomena Accompanying Insulin Therapy.—SEVRINGHAUS (*Arch. Neurol. and Psychiat.*, 1929, 22, 746) calls attention to the widespread effect and varying symptomatology of hyperinsulinism ranging from effects on the vegetative nervous system such as vasomotor disturbances (due largely, he believes, to stimulation of the adrenal glands), through sensory phenomena and motor disturbances such as hemiplegias, paraplegias, tremor and even convulsions, to mental phenomena such as restlessness, coma, loss of inhibitions, emotional disturbances, hallucinations, amnesia, aphasia, peculiar confusional states, catatonia and negativism. He cites one case of hyperinsulinism which was mistaken in a hospital for alcoholism. He finds that there is nothing specific about the picture except the circumstances under which it is induced, but that in a given patient it tends to run more or less true to type, hence he believes that when a patient knows how hyperinsulinism affects him he is more or less true to type, hence he believes that when a patient knows how hyperinsulinism affects him he is more or less protected. "The variability of sequences in persons is not more surprising than the variability in response to any other stimulus capable of as wide an effect as hypoglycemia can have. The only conditions to be compared with it are carbon monoxid poisoning or any other type of anoxemia, alcoholic intoxication, thyrotoxicosis, cerebral vascular accidents, epilepsy, uremia and dementia, particularly of the catatonic type. These are the conditions with which reactions to insulin are apt to be confused. In diagnosis of coma without a history, the possibility of a coma due to hypoglycemia must be considered. If an analysis of the blood cannot be secured at once, it should be remembered that the therapeutic trial of dextrose given intravenously is never dangerous and may be saving. . . . A single dose of sugar will never cause a diabetic person to develop coma. It should be used without hesitation when hypoglycemia reactions occur."

Hyperpyrexia Produced by Baths.—MEHRTENS and POUPPIRT (*Arch. Neurol. and Psychiat.*, 1929, 22, 700) report on the experimental production of febrile temperatures by the use of continuous baths. The technique of producing hyperpyrexia was, briefly, as follows: Patient was immersed in bath at 110° F. and the temperature of the bath was maintained until the temperature of the patient reached a point within 1½ degrees of the fever desired. Then the temperature of the bath water was gradually reduced until it corresponded with the temperature of the patient. Ordinarily the bath lasted one hour but it was possible to maintain the patient's fever for another hour by wrapping him in

blankets and placing a few hot-water bottles in the bed. "Liquids may be administered by mouth but they must be hot." The baths were administered, as a rule, once a day, occasionally twice a day and at time every other day or every third day. Following the baths the patients felt fatigued but many were able to walk to their rooms. There was a loss of 3 to 5 pounds which was regained by the next morning. (Most of the patients had gained in weight at the end of a series of 14 baths.) There was a regular increase in the pulse. The blood pressure usually fell with an average reduction of 50 mm. systolic and 20 mm. diastolic, with the pressure rising to its former level in twenty-four hours. In rare instances there was an increased systolic pressure. Basal metabolic rate increased from 80 to 100 per cent. Hemoglobin and red cell count tended to show increases with an increase in reticulocytes from 2 to 3 per cent. They noted the following psychologic reactions: In baths at temperature between 98° and 102° the patients were calm and coöperative; between 102° and 103° they frequently showed signs of restlessness and anxiety; from 103° to 105° they were quieter and rather apathetic; and between 105° and 107° mild confusion frequently occurred lasting in unusual cases for an hour after the patient's return to bed. Following a series of baths there was a frequent diminution of the Wassermann reaction in the cases with syphilis and the parietic types of gold curve tended to change to the tabetic types. These serologic changes usually came on rapidly, frequently within a month of completion of the series of baths. They found that the permeability quotient of the meninges was lowered in all cases when the temperature was greater than 103° F. and continued for at least thirty minutes and repeated on at least five successive days. With 11 parietics, 2 recovered sufficiently to return to work, 4 showed marked clinical improvement, 3 showed slight improvement and 2 were unimproved. Psychometric ratings did not demonstrate improvement after treatment even in the patients able to return to work. The spinal fluid serology was improved in 6 cases. With 20 tabetics every patient was improved in some way and this was particularly true of the "burnt-out" cases showing no positive changes in the spinal fluid. Lightning pains, gastric crises and Charcot joints yielded to hot baths more readily than any other therapy they had previously used. Nine cases of encephalitis did not show generally favorable results. Tremor, spasticity and ocular crises tended to be modified. Relapses after treatment was discontinued were common. Three cases of combined sclerosis showed transitory improvement. A miscellaneous group of patients complaining of pain were markedly improved by the baths. Amyotrophic lateral sclerosis showed no improvement. Excited, psychotic patients tended to have a sedative effect from the baths which were generally followed by restful sleep. The authors conclude that in treating syphilis the malaria therapy is simpler, requires less coöperation on the part of the patient and may have valuable factors in the toxemia produced apart from the fever. On the other hand fever produced by baths is under perfect control, can be maintained at any degree for any length of time up to two hours, may be applied at any time or at any interval, and may be continued daily for at least six weeks, while the patient still gains in weight and maintains his strength. They do not interfere with antisyphilitic therapy of other types and tend to intensify the therapeutic effect of antisyphilitic medication.

PATHOLOGY AND BACTERIOLOGY

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The Pathologic Anatomy in Twenty-eight Cases of Addison's Disease.
—Cases of Addison's disease have been reported as the result of a variety of lesions of the suprarenal body. BARKER (*Arch. Path.*, 1929, 8, 432) presents autopsy data from 28 cases of Addison's disease. Among these, bilateral tuberculosis of the suprarenal glands was found in 25 cases, and advanced bilateral suprarenal atrophy in 3 cases. Acid-fast bacilli were demonstrated in 11 of the 25 tuberculous cases. In all the cases but one, some suprarenal tissue remained, the maximum amount being estimated at 10 per cent of normal. Seventy-three cases are also presented in which there were suprarenal lesions but in which there was no clinical evidence of Addison's disease. In these cases the estimated amount of suprarenal tissue remaining was never less than 10 per cent of normal. In only 10 cases was more than 75 per cent of the tissue apparently destroyed.

Experiments to Determine Whether There is a Filtrable Form of the Tubercle Bacillus.—The very conflicting evidence regarding the existence of a filtrable form of the *Bacillus tuberculosis* prompted GLOYNE, GLOVER and GRIFFITH (*J. Path and Bact.*, 1929, 32, 775) to make a careful study of the problem. Filtrates from 26 tuberculous sputa prepared in various ways, produced no tuberculous lesions when injected into 50 guinea pigs. Nine guinea pigs, inoculated with filtrates of uterine, placental, or fetal materials taken from tuberculous women, showed no evidence of tuberculosis. Histologic sections confirmed the macroscopic findings. Complement fixation tests made at the time of death with the blood sera of the guinea pigs were positive in two instances and negative in fourteen. Filtrates prepared from tuberculous lesions in various organs of men, monkeys, rabbits and cattle, representing six human and three bovine viruses, were inoculated into 26 guinea pigs and one rabbit. None of these showed gross or microscopic evidence of tuberculosis when subsequently killed. Cultures of the filtrates used in inoculation remained sterile. Filtrates of avian viruses were tested on three fowls and one rabbit, all of which remained healthy. Tuberculin tests upon the inoculated animals taken just before termination of the experiments were uniformly negative. The occasional occurrence of doubtful lymph gland enlargement at autopsy was tested by the inoculation of 8 guinea pigs, all of which remained free from tuberculosis. In the experience of these authors false positive results could be obtained when jointed connections were used in the filtration apparatus.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Respiratory Immunity in Rabbits. VIII. Rabbits Immunized with Pneumococcus Types II, III and IV Resist Intranasal Infection with Type I.—The hope of obtaining a curative serum for pneumonia has been the chief motive power in the vast amount of work that has been done on the antigenic constitution of the pneumococcus. It was such an interest that led Neufeld to discover the fact that the serum of an animal which had been immunized with a certain strain of pneumococcus would confer passive protection against infection with this strain and also against certain other strains but not against all strains. BULL and McKEE (*Am. J. Hyg.*, 1929, 10, 229) claim that the fact that active immunity to the pneumococcus is not entirely type specific is of interest from a practical point of view, namely, in connection with the prophylactic vaccination of man. Vaccination against the three fixed types offers no great difficulty but the very heterogeneous nature of Group IV organisms makes it practically impossible to have all serologic types represented in a vaccine. If man reacts to pneumococci as rabbits do, it seems that vaccination with any type of pneumococcus should protect against natural infections with any other type. Rabbits immunized with pneumococcus Types II, III or IV are completely resistant to intranasal infection with Type I organisms and also manifest considerable resistance to intravenous infection with the same types.

On the Natural Immunity to Scarlet Fever of the Japanese and Chinese Residing in South Manchuria.—ANDO, NISHIMURA and OZAKI (*J. Immunol.*, 1929, 17, 473) state that according to the Dick skin test there is a considerable difference in the susceptibility to scarlet fever between the Japanese and the Chinese residing in South Manchuria. The difference in scarlet fever morbidity of these two races may at least be partly explained by the difference in their susceptibility. No fact has been discovered which seems to indicate that there is a greater percentage of negative reactors among Japanese children who lived long or were born in Manchuria where scarlet fever is more prevalent than in Japan proper than among those who lived long in Japan proper and have immigrated only recently. It seems reasonable to suppose that the difference in susceptibility may indicate racial difference of "Antikörperbildungsbereitschaft" in the sense of Hirzfeld, but not dependent on the difference in "Umwelteinflüsse."

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 17, 1930

The Determination of the pH of Serum with the Quinhydrone Electrode.—E. P. LAUG and D. WRIGHT WILSON (from the Department of Physiological Chemistry, University of Pennsylvania). On account of the difficulty of determining pH of body fluids by the hydrogen electrode, and certain errors encountered with the use of the colorimetric method, it seemed desirable to study the quinhydrone electrode in the hope that it might prove to be sufficiently simple and trustworthy for the pH determination of serum and plasma. A capillary quinhydrone electrode chamber was used, requiring 1 cc. serum. All determinations were done at 38° and checked with the hydrogen electrode. Considerable drift with the quinhydrone electrode occurred, but satisfactory determinations could be obtained by extrapolation. Individual extrapolated readings checked among themselves within 0.02 to 0.03 pH. In 34 determinations on the sera of 13 dogs, the quinhydrone electrode was found to average 0.02 pH more acid than the hydrogen electrode. The maximum spread of this acid correction amounted to 0.08 pH. The maximum deviation from the average amounted to 0.04 pH. Various experimental procedures caused no variation in the quinhydrone correction. It may therefore be concluded that the quinhydrone electrode may be used for pH determinations of blood serum with sufficient accuracy for most purposes.

The Effect of Irradiated Ergosterol on the Absorption of Calcium from the Gastro-intestinal Tract.—By J. H. JONES, M. RAPOPORT and H. HODES (from the Department of Physiological Chemistry, University of Pennsylvania). Recently it has been shown by numerous investigators that large doses of irradiated ergosterol produce a marked hypercalcemia. The source of this excess calcium has not been determined. If it comes from the body tissues it should be possible to increase the concentration of this element in the serum even though there were no calcium in the food, but if the additional calcium comes from the intestinal tract, it should be impossible to produce a hypercalcemia on a calcium-free diet.

Thirteen dogs were each given approximately 1 mg. of irradiated ergosterol per kilo per day. Seven of the animals were used as controls and were fed a diet containing about 0.25 per cent calcium, and the other six were fed a diet practically calcium free. At the end of two weeks the concentration of calcium in six of the controls ranged from 15.43 to 17.75 mg. per 100 cc. of serum, and that of the remaining control animal was 12.63 mg. The dogs on the calcium-free diet were given the ergosterol for about three weeks instead of two, at the end

of which time the concentration of calcium in five of these animals ranged from 12.41 to 13.25 mg. per 100 cc. of serum. Analyses during the three weeks period showed a very slight increase in concentration of calcium. A rather marked hypercalcemia was produced in one of the animals on the calcium-free diet, the concentration being 15.75 mg. per 100 cc. of serum at the end of the period.

Of the five animals which showed little or no hypercalcemia in three weeks, one was given "klim" and yeast at the time the ergosterol was discontinued, and daily thereafter. In six days the concentration of calcium was 15.92 mg. The other four animals were each given 20 gm. of calcium gluconate by stomach tube and in twenty hours the concentration of serum calcium ranged from 15.50 to 17.56 mg. per 100 cc. One control experiment showed no hypercalcemia at the end of twenty hours after the administration of a similar amount of the calcium salt to a dog receiving no ergosterol.

These data would indicate that the excess calcium of ergosterol hypercalcemia comes from the food, the absorption of which is increased under the influence of this drug. However, the possibility of decreased elimination has not been ruled out.

The Specific Cytotoxic Action of Tuberculin on Tissue Culture.—JOSEPH D. ARONSON (from the Henry Phipps Institute, University of Pennsylvania). The specific cytotoxic action of tuberculins prepared from the various acid-fast bacteria upon the bone marrow and the spleen of tuberculous and of nontuberculous guinea pigs was studied by means of tissue culture.

It was found that bone marrow and spleen of tuberculous guinea pigs when planted in plasma from tuberculous or nontuberculous guinea pigs fail to migrate and to multiply in concentrations of tuberculin prepared from the human or bovine type of tubercle bacillus, which also does not interfere with the migration and multiplication of the bone marrow or spleen of the nontuberculous animal. When high dilutions of tuberculin are added to bone marrow or spleen of tuberculous guinea pigs migration of cells occurs but the cells are shrunken and rounded, whereas the cells of tissue from the nontuberculous animals are irregular, larger and vesicular.

Tuberculins prepared from the avian type of tubercle bacillus, from the different acid-fast bacilli found in fish, snakes, frogs and turtle, from several different strains of the lepræ bacillus and from a number of different acid-fast saprophytes, did not interfere with the migration and multiplication of the cells from the bone marrow and from the spleen of tuberculous or of nontuberculous guinea pigs.

The specific sensitivity to tuberculin prepared from the human or bovine tubercle bacillus cannot be transferred to tissue from nontuberculous guinea pigs by the addition of plasma from a tuberculous animal.

The Action of Ultraviolet Rays on Sea-urchin Egg Protoplasm.—L. V. HEILBRUNN (from the Department of Zoölogy, University of Pennsylvania). In a recent monograph, I have attempted to show that when protoplasm is aroused to activity, one aspect of the response is a decided increase in viscosity. Both my older results and those of

other investigators have shown, in every case that has been suitably studied, that all protoplasmic stimulants cause such a viscosity increase. Furthermore this viscosity change is believed to be the result of a reaction (or series of reactions) which may be demonstrated to occur in widely different types of living substance, a reaction in many ways similar to that of blood clotting. This reaction, which I have called the surface precipitation reaction, typically requires calcium in its early stages.

Some years ago, Lillie and Baskervill found that the sea-urchin egg could be stimulated to divide by exposure to ultraviolet radiation. In experiments now reported on, I was able to show, (1) that such exposure to ultraviolet radiation produced a marked viscosity increase, and (2) that the radiation was only effective in the presence of calcium. Numerous tests with oxalated eggs showed complete absence of stimulation. Such eggs were not injured, and upon being returned to sea water and exposed to ultraviolet radiation, they showed the typical stimulation effect.

Some Results from Synchronization of Roentgen Ray Films of the Lung.—F. MAURICE MCPHEDRAN (from the Henry Phipps Institute, University of Pennsylvania, Philadelphia). A synchronized Roentgen ray film of the lungs is an exposure made at a certain phase of the cardiac cycle. Synchronized films may be roughly divided into those that are systolic and those that are diastolic. With exposures of usual length, about one-tenth second, systolic films show blurring of the cardiac margin and of the trunk markings in the areas beside the heart, whereas in diastolic exposures the cardiac margin is sharply defined and the trunk markings are relatively clear-cut. Decrease of the length of exposure improves the sharpness of definition of both systolic and diastolic films, particularly the former, but only in patients with emphysema does the number and sharpness of the vessels recorded approach that of the excised lung. Although this appearance is no doubt partly referable to decreased density of the parenchyma relative to the density of the vascular arborization, it seems possible, from comparisons with differing techniques on young boys with thin chest walls, that change in the pulmonary elasticity is also a factor. This is also suggested by the fact that of diastolic exposures of the same person, those made with the slower heart rate show sharper pulmonary detail.

Synchronization constantly produces films more accurate than otherwise obtainable, pairs of films that are truly stereoscopic and series of films that are truly comparable. Accurate recording of pulmonary detail is conspicuously of value (1) because it gives a criterion for the comparison, from month to month, of the relative density of early lesions based on the pleura (for example, adolescent tuberculosis); (2) because upon and between the pulmonary markings, particularly in the base, appear the infiltrations of the childhood type of tuberculosis and nontuberculous lesions at all ages. In the discovery and supervision of these basal lesions, particularly the slighter ones, accurate comparable and truly stereoscopic films are essential. Synchronizing both exposures to occur in diastole affords stereoscopy of the cardiac and paracardiac areas and permits recognition of slight infiltrations

that appear as spots upon or between the vascular markings or, in the more chronic stages, cause irregular emphasis and distortion of vascular detail. Without control of the time of exposure with relation to the cardiac phase, truly stereoscopic films are a matter of chance. Even a small amount of cardiac movement, as revealed by a blurred heart border, may render a small infiltration wholly imperceptible.

Synchronization provides films that may be compared with and interpreted in the light of pathologic study of excised lungs that have been Roentgen rayed while inflated. It has made it possible define the limits of recordability of enlarged nodes within the hilum and, in eliminating artefacts due to movement, has clarified many confusing appearances.

In summary, synchronization has proved of material aid in adapting the Roentgen rays to the discovery of changes in pulmonary density. Except when wholly hidden by opaque structures, such as heart and diaphragm, and this is unusual, synchronized stereoscopic films record, with fair accuracy those pathologic changes of the parenchyma that are sufficient to be the cause of symptoms and also latent lesions. Furthermore, they assist in defining the pathologic structure and direction of change of tuberculous and most nontuberculous infiltrations, and they are, therefore, a record of the anatomical stability of a lesion, without which arrest and cure are illusory.

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ORIGINAL ARTICLES.

MYXEDEMA DURING THE ADMINISTRATION OF IODIN IN
EXOPHTHALMIC GOITER.*

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WITH the exception of the case reported by Haines¹ and referred to by Plummer,² we know of no instance of typical myxedema attributed to the administration of iodine.

In a previous study of low basal metabolism following thyrotoxicosis^{3,4,5} we observed that the temporary administration of iodine sometimes produced a temporary low metabolic rate.³ In none of these instances, however, was there sufficient clinical evidence to justify a diagnosis of myxedema. The data suggested that in some cases the low metabolism might be normal for the patients, while in others it might represent an underfunction of the thyroid which did not last long enough to become evident upon physical examination. About a year and a half ago, one of the patients reported in this study returned to the clinic after a considerable absence com-

* This study was aided in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

plaining that her eyes had not completely returned to their pre-goiter size. Otherwise she appeared normal. For her persistent exophthalmos she was given iodine. During each of two courses of this medication her basal metabolism slowly dropped to a low level, and, in association with this, she developed typical myxedema. This cleared up promptly and her basal metabolic rate rose to normal either when iodine was omitted, or when iodine was continued and desiccated thyroid given in addition.

In two other patients myxedema was associated with the post-operative administration of iodine. In one, iodine appeared to be the cause of the myxedema. In the other, it accentuated a mild post-operative myxedema. In the latter patient before operation, and in another patient who has never been operated on, iodine produced a syndrome suggestive of myxedema.

Data. The data on the 4 cases are given in histories and figures.*

In the following patient there is no doubt that typical myxedema was produced at least twice by the postoperative administration of iodine:

Case reports. CASE I.—(Fig. 1.) Lab. No. 3543. Miss B. B., a Jewish housemaid aged eighteen years, entered this hospital October 8, 1925, having typical exophthalmic goiter of moderate severity with marked exophthalmos. Her basal metabolism ranged from +37 to +44. On Lugol's solution it promptly fell to +14 and she improved symptomatically. October 22 a subtotal thyroidectomy was performed. November 5, when her metabolism was -9, Lugol's solution was started in a dose of 8 drops daily. During its administration her metabolism gradually fell until on January 6, 1926, it was -25. At this time her face was round and slightly puffy and she appeared a little slowed up. The evidence was not considered adequate, however, to make a diagnosis of myxedema. Iodine was then omitted. Her metabolism rose to standard normal and for the next ten months, for the most part on combined iodine and thyroid medication, maintained the course shown in Fig. 1.

She was not seen subsequently for about a year. On returning to the hospital December 28, 1927, her basal metabolic rate was +25 and this raised the question of residual thyrotoxicosis. On frequent successive tests, however, her metabolism, without medication, fell to normal. As far as could be determined clinically she had no thyrotoxicosis. She was a very active individual and had a moderate residual bilateral exophthalmos (more on the right than on the left) and slight lid lag on the right, but there was no tremor, excess sweating, weakness or undue nervousness. There was a pea-sized nodule of palpable thyroid tissue on the left side of her neck.

On January 26, 1928, 2 drops of Lugol's solution daily was started, in order to try its effect in reducing the exophthalmos. The first subsequent low basal metabolism (-17) was noted April 12. Her voice had become somewhat hoarse, and about this time she began to feel a little listless and sleepy in the daytime. April 26 (basal metabolic rate still -17) her skin was noted to be a little rough and dry. By May 10 her metabolism was -25 and the myxedema was typical. She was markedly apathetic, drowsy and slowed up, and her muscles tired very easily on exertion. She had gained 4 kg. in weight since starting iodine, her face had become puffy and her skin

* All basal-metabolism determinations were made with the Benedict-Roth apparatus, and Aub-Du Bois standards were used in the calculations.

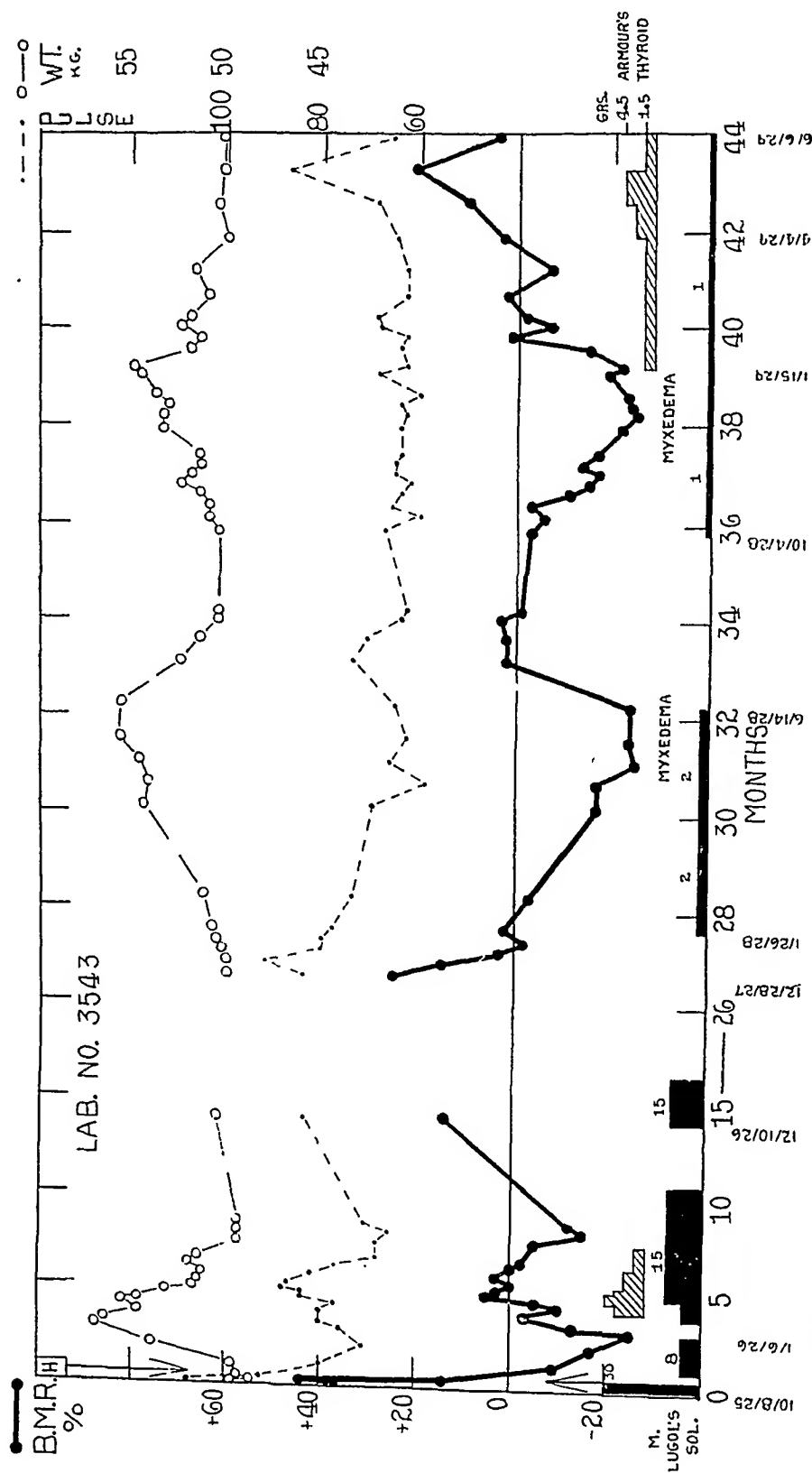


FIG. 1.—Case I. The development of typical myxedema during administration of iodine, two and a half and again three years after subtotal thyroidectomy (arrow) for exophthalmic goiter. At the time of the first low basal metabolism on iodine shortly after operation the clinical evidence was not sufficient to make a diagnosis of myxedema. In this and subsequent charts, the black areas denote periods of treatment with compound solution of iodine and the cross-hatched areas, periods of treatment with Armour's desiccated thyroid.

harsh and dry. Her speech was slow and thick and her voice hoarse. She was extremely sensitive to cold. She continued thus for about another month and a half, gaining another kilogram in weight.

Iodin was omitted June 14. The basal metabolism rose to within normal limits by July 12. The puffiness of her face disappeared, she lost 3.2 kg., her skin became soft and smooth, her hoarseness practically disappeared, she talked much faster and was once more her lively, energetic self. There were no symptoms of thyrotoxicosis. Her exophthalmos had been little affected by iodine, however. Except for a loss of 2 more kilograms in weight, her clinical condition remained the same for about three months.

One drop of Lugol's solution daily was started October 4, 1928. The effect on basal metabolism and clinical symptoms was similar to that resulting from the previous course of Lugol's. It was November 1 before her basal metabolism had fallen to -15 . At this time the symptoms of myxedema were just developing. By December 6 her rate had dropped to -22 , and not until then was the myxedema typical. More care was taken this time to make notes about changes in the thyroid gland remnant. One month after the previous course of Lugol's was omitted there was a cherry-sized mass of thyroid tissue in the isthmus and one in the left lobe. After being on Lugol's solution for three weeks, each thyroid nodule was a little harder and firmer but was still about the same size. Three weeks later the nodules were only pea-sized. A little over two months after starting 1 drop of Lugol's the tissue was barely detectable, that is, much smaller in amount than just after starting the medication.

January 15, 1929, after she had been on 1 drop of Lugol's solution daily for a little over three months, and had gained 4.7 kg. in weight, instead of omitting the iodine, $1\frac{1}{2}$ grains of Armour's desiccated thyroid was given daily in addition. This had the same effect as omitting Lugol's. The basal metabolism rose to normal by January 31 and the signs and symptoms of myxedema disappeared. She lost 3.6 kg., her skin desquamated all over her body and her hair fell out markedly. The change in personality was so striking that her mistress remarked on the increased speed and energy with which she did her work.

April 4 when her metabolism was $+3$, thyroid was increased to 3 grains daily. April 25 her rate was $+10$, and she was apparently well. Thyroid was then increased to $4\frac{1}{2}$ grains daily. May 16 her metabolism was $+21$ and her pulse rate had risen from 69 to 87. She was nervous and irritable and acted as if she were "on edge." Sweating was increased. There was no tremor. One of the people with whom she lived thought her eyes protruded a little more, but we could not be certain of any definite change when she was seen in the hospital. Thyroid was reduced to $1\frac{1}{2}$ grains daily. June 6, 1929, when last seen, her basal metabolism was $+4$ with a pulse rate of 66. She was less nervous and irritable and perspired less. She showed no symptoms of thyrotoxicosis or of myxedema. There was no palpable thyroid tissue.

In the following patient a mild myxedematous condition which developed shortly after a subtotal thyroidectomy was accentuated by iodine, and the evidence suggests that myxedema also developed during one of the three preoperative administrations of iodine:

CASE II.—(Fig. 2.) Lab. No. 4675. Mrs. E. C., a housewife, aged thirty-five years, with mild exophthalmic goiter, was first seen in this clinic April 7, 1927, when her basal metabolic rate was $+22$. She was nervous, fatigued easily, had palpitation and was losing weight; her skin was warm and moist and showed marked dermatographia; she had a tremor

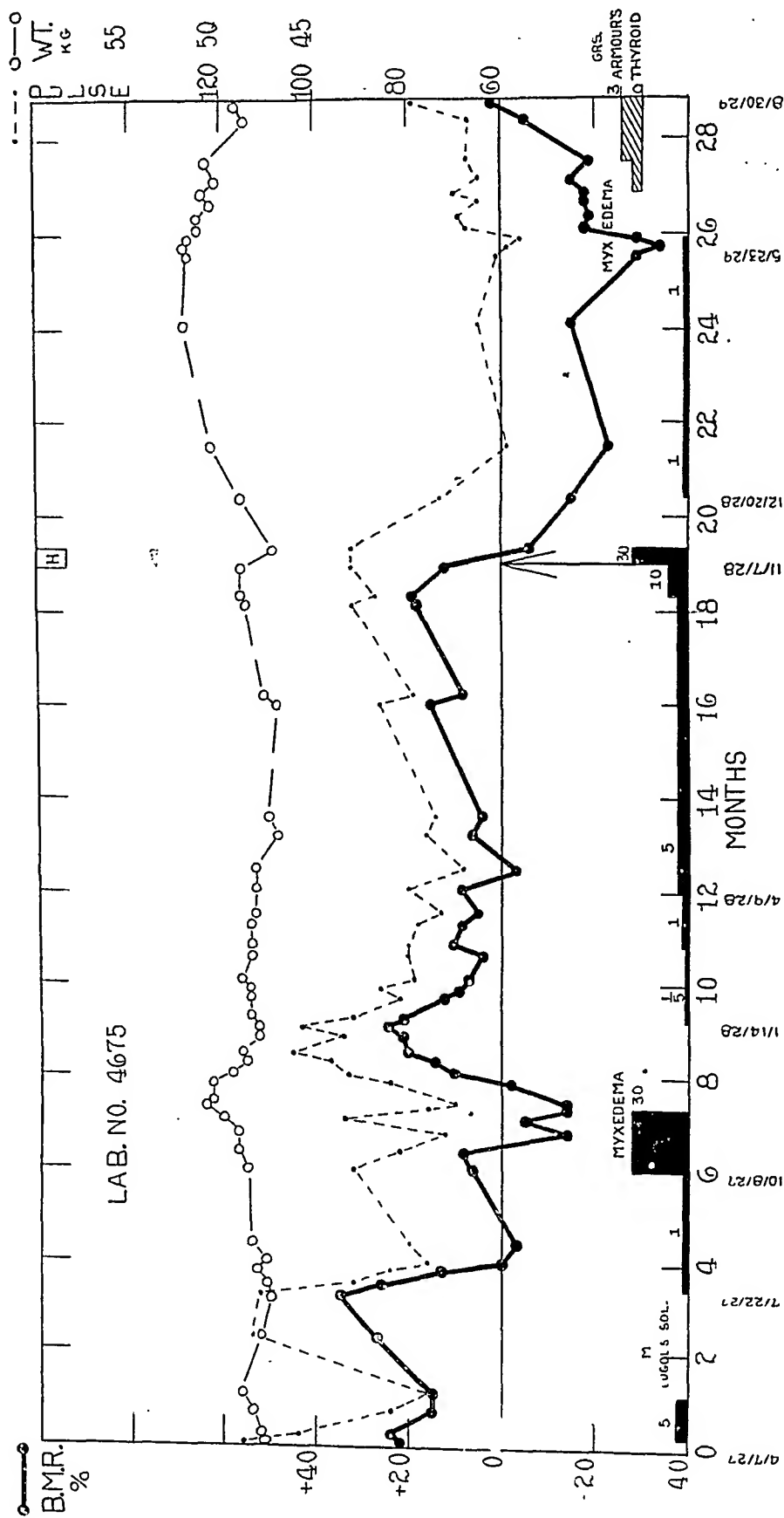


Fig. 2.—Case II. The development of myxedema during administration of iodine in a patient with exophthalmic goiter before a subtotal thyroidectomy (arrow) and the accentuation of myxedema during iodine administration after operation.

and slight exophthalmos with lid lag; her thyroid was very slightly enlarged, rather firm, and there was a slight bruit over it. Lugol's solution, 5 drops daily, was started April 13, but produced no significant change except for some decrease in palpitation and pulse rate. On omission of iodine (May 11) the disease became a little worse, however.

One drop daily of Lugol's solution was started July 22. By August 6 her metabolism had dropped from +26 to zero. She was less nervous and had less palpitation. Her thyroid had grown larger since starting iodine and was moderately firm. She continued about the same and Lugol's was increased to 30 drops daily on October 8, when her metabolism was +6. During November her metabolic rate was for the most part at a level of -15. She had gained 3.1 kg. since starting Lugol's. She developed puffiness under her eyes, complained of transient swelling of her hands and feet, and felt very tired and drowsy all the time. Her voice was hoarse in spells, her hair was falling out markedly and she was unusually sensitive to cold. She felt much calmer however, and her heart pounded less. Lugol's was omitted November 17. December 2 her metabolism was -2 per cent and on December 9, +10. Her eyelids were less puffy, and she had more palpitation. January 14, 1928, her metabolism was +21, she had lost 2.4 kg. in weight, and the symptoms suggestive of myxedema had been replaced by those of mild thyrotoxicosis. Her thyroid was softer than when she was taking iodine.

Iodine was then resumed. By February 3 her metabolic rate had dropped to +9 and remained at a normal level, with some clinical improvement, until August 7, when it had risen to +15. October 17 it was +19 and the symptoms of thyrotoxicosis had increased. Her thyroid had become harder on iodine but no increase in size was noted. On November 7, 1928, she underwent a subtotal thyroidectomy. Iodine was omitted November 17. December 20, about one month after discharge from the hospital, her metabolism was -15. Symptoms of thyrotoxicosis had practically disappeared except for nervousness, which, however, was decreased. There was no clinical evidence of myxedema.

Lugol's solution, 1 drop daily, was started December 20. During its administration her metabolic rate dropped from -15 to about -30 by June 3, 1929, as shown in Fig. 2. April 11 she was feeling well, but by May 23 she was complaining of feeling very cold, sleepy, exhausted and ambitionless all the time. Her skin was a little rough and dry, her face was puffy, and her voice became hoarse. Induration about the scar had diminished and it was thought that a thin piece of thyroid tissue about 1½ inches long could be felt on the left side of the neck. Her condition remained unchanged until June 3, on which date Lugol's was omitted.

From June 12 to July 3 her basal metabolism was -18. She felt little better subjectively, but her skin began to peel, her face was less puffy and her voice less hoarse. Her hair had been falling out since operation. From July 3 to July 22 Armour's thyroid was administered in a dose of 1½ grains daily. This did not affect her metabolism significantly, but by July 9 she had begun to have more energy, a better appetite, to sleep better, be less discouraged and to have still less puffiness of the face. She still felt cold most of the time, however, and her hair continued to fall out. July 22 the dose of thyroid was increased to 3 grains daily. By August 20 her basal metabolism was -5. She was much more lively, less sleepy, tired much less easily, and the puffiness had completely disappeared from her face. She was still a little nervous and had some backache, however. By August 30, her metabolism was +2. There was little subjective or objective change. There was no palpable thyroid tissue. The myxedema had completely disappeared.

It appears reasonably certain that the following patient had mild myxedema during the postoperative administration of iodine, but the evidence is less definite than in the two preceding cases. The cause of the slight depression of the basal metabolism which occurred subsequent to the omission of iodine can be explained only by the future clinical history of the patient. It is possible that it was due to an underfunction of the thyroid which was so mild that it could not be detected clinically:

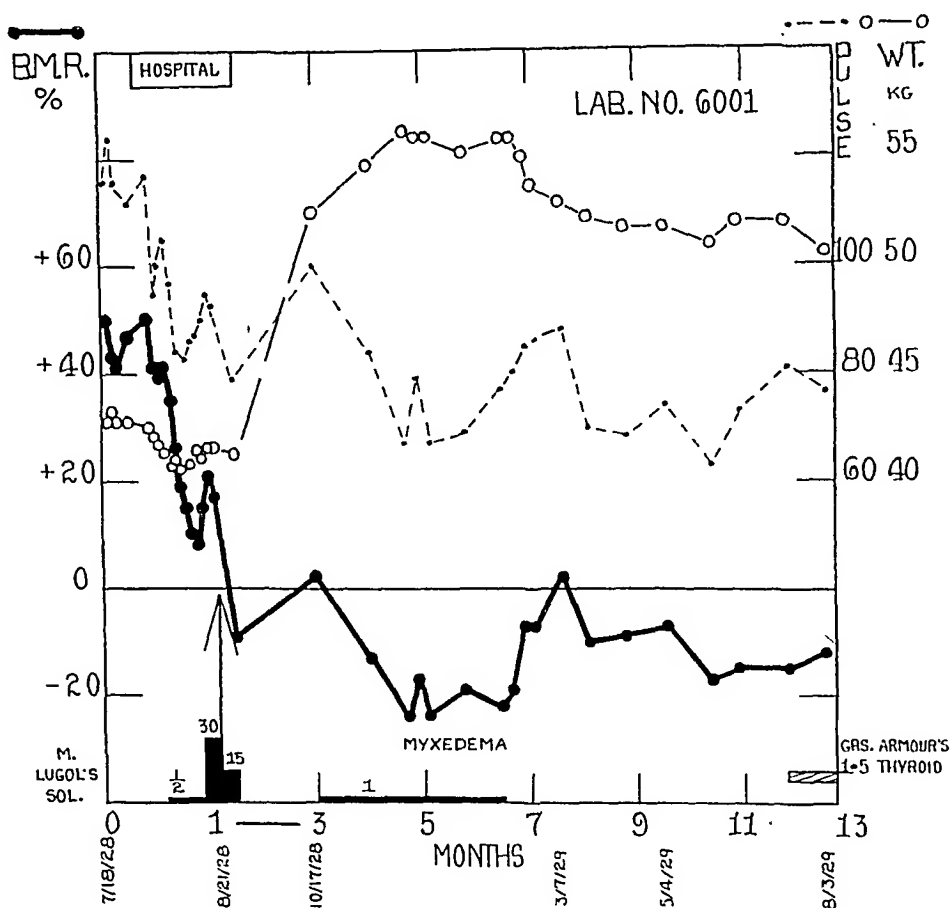


FIG. 3.—Case III. Temporary mild myxedema coincident with temporary administration of iodine, following subtotal thyroidectomy (arrow) for exophthalmic goiter.

CASE III.—(Fig. 3.) Lab. No. 6001. Miss E. M., a schoolgirl, aged sixteen years, had moderately severe exophthalmic goiter. Her basal metabolic rate responded to iodine medication pre-operatively with a fall from +50 to +17. There was coincident improvement in clinical symptoms. A subtotal thyroidectomy was performed August 21, 1928. She was discharged from the hospital much improved on September 1, at which time iodine was omitted.

One drop of Lugol's solution daily was started October 17, 1928. At this time she had no thyrotoxicosis and was apparently normal symptomatically, with a basal metabolism of +2. Her exophthalmos had disappeared, her skin was normal and her face, though full, was not puffy. By December 8 her metabolism had gradually fallen to -24. She did not have her normal

amount of energy and ambition and she minded the cold a great deal. She had gained 3.7 kg. in weight and had developed some puffiness under her eyes. Her skin was a little dry and her hair was falling out. Her voice was husky, but this may have been a result of a paralysis of the right vocal cord which was noted just after operation.

Her clinical condition continued about the same until Lugol's was omitted February 2, 1929. By February 15 her metabolism had risen to -7 . For about a week she had noted a marked change in herself. She had much more energy, vivacity and ambition. Her appetite was better. She wanted to be active all the time, whereas, while on Lugol's, she was contented to sit around the house and read. She was still slightly hoarse, had slight puffiness under her eyes and minded the cold. Her hair was falling out markedly. By March 7 her rate was $+2$. Her eyelids were less puffy, her voice, though slightly hoarse, was much less so than it had been when she was on Lugol's. She looked much thinner, although she had lost only 3 kg. since omitting iodine. She continued to feel more lively and energetic and minded the cold less. March 21 her rate was -10 . New hair was growing in rapidly. Her skin was soft and smooth. April 11 and May 4 her basal metabolism was -9 and -7 respectively. She felt very well. She was never tired and was "on the go" all the time. Her hair had almost stopped falling out, her skin was normal and she did not mind the cold. She had lost 4.2 kg. since omitting iodine. There were no signs or symptoms of either thyrotoxicosis or of myxedema.

For some unknown reason, without any other apparent change, the basal metabolism dropped to about -15 and remained there from June 1 to July 13. There were no detectable signs or symptoms of myxedema, and the patient felt as well as when the metabolism was normal. Armour's thyroid was started July 13 in a dose of $1\frac{1}{2}$ grains daily. By August 3 the metabolism and clinical condition had not changed, except that she lost 1.6 kg. in weight.

The following patient, who was treated only by iodine, was probably mildly myxedematous at the time of her second low basal metabolism:

CASE IV.—(Fig. 4.) Lab. No. 5004. Mrs. M. P. W., a housewife, aged twenty years, when first seen August 2, 1927, had mild exophthalmic goiter with a basal metabolic rate of $+24$. She was nervous and irritable and was losing weight. Her eyes were stary and she had a slight tremor. The lobes of her thyroid were firm and moderately enlarged, more on the right than on the left, and the isthmus was markedly enlarged. There was a well-marked systolic bruit over both superior thyroid arteries, more marked on the right. She had been given iodine by a local doctor, but had had none for at least one month before coming to the hospital. Lugol's solution, $\frac{1}{2}$ drop daily, was started August 4. October 14 her metabolism was $+10$ and she had gained 2 kg., but there was no subjective change. Her goiter, after an initial enlargement on iodine, had become smaller and softer. Lugol's was omitted. Off iodine her metabolism ranged from $+30$ to $+47$. She lost about 2 kg. in weight, her skin became more moist and flushed, she was more nervous and restless and she developed some palpitation and dyspnea.

November 5, when her rate was $+35$, Lugol's solution was resumed, first in a dose of $\frac{1}{2}$ drop daily and then 1 drop daily. By January 21, 1928, her metabolism had fallen to -14 and remained at approximately this level until February 25. She gained 6.7 kg. in weight, was much less irritable and

nervous and felt unusually energetic. She did not mind the cold. Her lower eyelids were slightly puffy, but there was no other clinical evidence suggesting thyroid underfunction. Her thyroid was just slightly enlarged and there was no bruit or thrill over it.

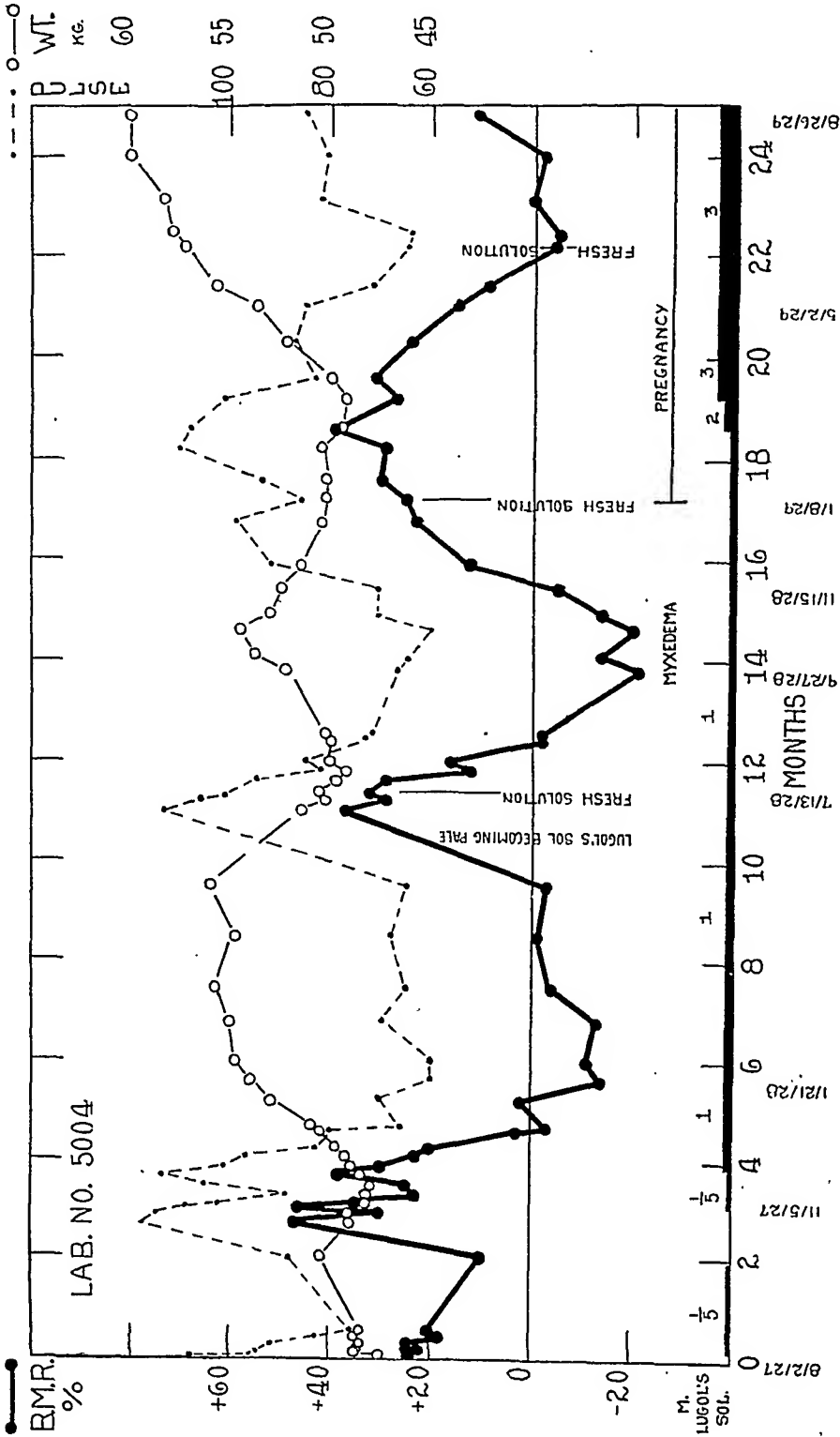


Fig. 4.—Case IV. The development of signs and symptoms suggesting mild myxedema during the second of two periods of low basal metabolism, which occurred during the continuous administration of iodine to a patient with otherwise untreated exophthalmic goiter.

While on the same dose of Lugol's solution, which solution however, was becoming much paler,* her metabolism started to rise. July 13 it was +32. Her thyroid had grown definitely larger and firmer and there was a bruit all over it, most marked at each superior pole. She had lost 4.5 kg. in weight, had a slight tremor, and her eyes were more prominent.

The old Lugol's was destroyed and fresh solution in a dose of 1 drop daily was administered. By July 27 her metabolism was +12. Her thyroid was smaller and softer, although the bruit was still marked. She had no tremor and seemed less nervous. By September 27 her metabolism had fallen to -21. She had gained about 2 kg. in weight and felt well. Whereas she had been very intolerant of heat during the early summer, she was now sensitive to cold. There was no other clinical evidence of myxedema. Her thyroid was about the same size. Her metabolism remained low until the end of October. By that time she had gained 2.4 kg. more in weight, and her skin had become a little dry on her hands. She had developed moderate puffiness of her eyelids, and seemed to be somewhat listless. Although naturally a woman who could do a great deal of work without undue fatigue, she then could not beat a cake without stopping for a rest and could sew only a short time before having to stop to rest her arm and finger muscles. Her thyroid was moderately firm and much smaller than when her iodine was weak. There was a bruit all over it.

While still on the same dose of Lugol's solution, which was essentially unchanged in strength, her metabolism began to rise. November 15 it was -5. Her weight had decreased a little over 2 kg. The numbness of her hands and the ease of fatigue of her arm muscles had completely disappeared. She looked and felt much more lively and there was practically no puffiness of her eyelids. Her metabolic rate continued to rise until, by December 18, 1928, it was +23, and associated with this rise there was a return of symptoms of mild thyrotoxicosis. Her weight was 4.2 kg. less than in October. Her eyes were more prominent than when her metabolism was low, she was a little nervous and irritable and got a little short of breath on exertion. Her thyroid became somewhat smaller and softer, and there was still a slight bruit over it.

She became pregnant the first part of January, 1929. In the next two months her metabolic rate rose further to +39, and her thyroid became a little larger. The dose of Lugol's was increased to 2 drops daily on February 21, and to 3 drops daily on March 7. Some time in April, as the morning nausea of her early pregnancy began to subside, her metabolism began to fall gradually. By May 2 it was +15 and by June 6 it was -4. At the same time her thyroid became smaller, until it was just slightly enlarged, her symptoms of thyrotoxicosis disappeared and she felt unusually well. Her basal metabolism remained within normal limits and her clinical condition remained unchanged up until the time she was last seen—August 26, 1929.

Discussion. The data from this and a previous study³ referred to above show that after a subtotal thyroidectomy for exophthalmic goiter, temporary iodine medication may produce a syndrome ranging from temporary typical myxedema to temporary low metabolism without accompanying signs and symptoms of myxedema. This makes it all the more probable that in many of the latter cases a thyroid underfunction which had not had time to become detect-

* At this time the patient's Lugol's solution was being kept in a cork-stoppered bottle. Under these circumstances a reaction takes place between the cork and the solution, as a result of which the cork is slowly destroyed and the solution becomes much paler. This does not occur if the solution is kept in a glass-stoppered bottle.

able clinically was responsible for the low metabolism. Such a theory has particular bearing on Case I (Fig. 1). As stated above, this patient was listed in the study of temporary low metabolism without myxedema (as Case V) on the basis of the data to that date. She had developed a basal metabolism of -25 on iodine shortly after operation, but there was not sufficient clinical evidence to justify a diagnosis of myxedema. On omission of iodine the metabolism rose to standard normal. In the light of the subsequent repeated development of typical myxedema on iodine, with the same depression of the metabolism as just after operation, there is little doubt that the first low rate was also due to a hypothyroidism which did not last long enough to manifest itself upon physical examination.

The fact that iodine may sometimes produce myxedema in patients who have been operated on for exophthalmic goiter, and that there is suggestive evidence that it may sometimes produce it in patients with untreated mild exophthalmic goiter, raises the question of the nature of the action of iodine in that disease.

Until recently it was Plummer's^{2,6} contention that in exophthalmic goiter the thyroid gland elaborates two products: (1) An abnormal product, presumably deficiently iodinated thyroxine, which accounts for the peculiar nervous manifestations of the disease which distinguish it from toxic adenoma, and which causes the portion of the increase in basal metabolism that can be controlled by iodine. (2) The normal hormone, which is produced in excess and which causes the portion of the increase in basal metabolism which cannot be controlled by iodine. He has recently modified his theory⁷ to the effect that all of the increase in basal metabolism may be due to excess secretion of the normal hormone, and that iodine may affect the secretion of both the normal and abnormal products.*

Haines¹ claims that the case he has reported supports Plummer's hypothesis. In this patient, a woman, aged twenty-eight years, myxedema with a basal metabolism of about -28 could be produced at will by the administration of iodine, following a subtotal thyroidectomy for exophthalmic goiter. The diagnosis of myxedema was based on intolerance to cold, edema of both eyelids, coldness and dryness of the skin and a "facies typically that of myxedema." When iodine was omitted the basal metabolism would rise to about -14 , the signs and symptoms of myxedema would disappear, and the patient would complain of nervousness and have a "stare characteristic of exophthalmic goiter." Because of these two findings (that is, nervousness and a stare) the patient was said to be suffering from exophthalmic goiter. A residual exophthalmos was apparently a constant feature and was little affected by the level of the basal metabolism. The author states "If, in this case, the

* A schematic representation of the effect of iodine on the thyrotoxicosis of exophthalmic goiter may be found in a paper by Means, Thompson and Thompson.⁸

phenomena of myxedema could be produced at will by the administration of iodine and by stopping it, these phenomena could be made to disappear and evidence of exophthalmic goiter substituted; we would then have proof of the coincident existence in this patient of both myxedema and exophthalmic goiter. Furthermore, almost incontrovertible evidence would be established in support of Plummer's hypothesis."

It is not clear to us how two conditions can coexist in the same patient if one disappears when the other is present. This difficulty is apparently partially overcome by later developments. While iodine was continued, sufficient desiccated thyroid was given to maintain a basal metabolism of about -6 . The patient then felt better than at any previous period of observation. Iodine was stopped and desiccated thyroid continued in the same dose. The basal metabolic rate rose in fourteen days to $+6$, the patient "became nervous and warmer, the eyes stared and puffiness of the lids of the type seen in exophthalmic goiter appeared." Inasmuch as relief from symptoms is supposed to have come only from the simultaneous administration of iodine and desiccated thyroid, the author concludes that "there was, then, absolute deficiency of thyroid secretion, and what secretion was present was partially of the character of that produced in exophthalmic goiter."

The evidence of myxedema in this patient appears much more definite than the evidence of exophthalmic goiter. In a patient who already has exophthalmos, a stare might well appear to be present in the alert expression that accompanies a normal level of metabolism, in contrast to the dull listless expression of the myxedematous condition. Slight nervousness may be due to many things.

All of the patients we have reported appeared to be in a healthy state and to present no evidence of exophthalmic goiter when they were not receiving iodine and their basal metabolic rates were at a normal level. In Case I the clinical picture produced by maintaining the basal metabolism at a normal level by the combined administration of iodine and $1\frac{1}{2}$ grains of desiccated thyroid (Armour's) was indistinguishable from that which was produced by causing the metabolism to rise to normal by omitting iodine. Moreover, when the metabolism was raised a little above the normal level by administering 3 to $4\frac{1}{2}$ grains of thyroid daily while iodine was continued, the clinical condition of the patient resembled that of Haines' patient when the basal metabolism was raised to $+6$ by administering thyroid and omitting iodine. Symptoms of thyroid intoxication from overdosage are not infrequently seen in patients with myxedema, even though the metabolic rate is within standard normal limits.⁵

Thus, so far as we were able to determine clinically, the administration of iodine to our patients caused a diminution in the secretion of what appeared to be the normal thyroid hormone. Inasmuch as iodine may produce this phenomenon, there seems to be no necessity

at present for postulating an abnormal thyroxin to explain the high basal metabolism in exophthalmic goiter.

The actual mechanism by which the reduction in basal metabolism is accomplished is, of course, unknown. Marine's⁹ theory that storage of colloid by virtue of the pressure it exerts inhibits cell function and interferes with secretion of the hormone, is a plausible explanation. It does not appear to explain some things however—for example, in a patient with exophthalmic goiter in whom a resting level of basal metabolism has been obtained, as little as 1.5 to 6 mg. of iodine will sometimes cause a drop in basal metabolism within twenty-four hours.¹⁰ In such a short time, even though an increase in colloid may occur, as has been shown by Marine and Rogoff,¹¹ it seems unlikely that sufficient would be stored on such small doses of iodine to cause "pressure retention." There is the possibility, however, that a sudden slight increase in colloid may be adequate to initiate the change. Although the gland in both Case IV and Case I initially became a little firmer after iodine was administered, at the time of the low metabolisms it was smaller, and at least in Case IV softer, than before iodine was given. In Case IV the first relapse on iodine was associated with some increase in size and hardness.*

While in some of the cases the low basal metabolism can be maintained for long periods (about three months in Cases I and II and about two months in Case III) and perhaps indefinitely on iodine, in others it cannot (Case IV). These variations in the length of time the depression of the metabolic rate can be maintained by iodine appear to be similar to variations that occur at higher levels of metabolism. The first relapse on iodine in Case IV could be attributed to weakening of the iodine solution, but the second such relapse did not have this complicating factor. The condition apparently changed spontaneously from one of mild myxedema to one of mild thyrotoxicosis while iodine was being administered in the same dose. Marine's theory could account for this by assuming that after a time the gland became accustomed to working under increased tension and the effect of iodine wore off. In addition to the objections to this hypothesis enumerated above, it may be said that while it might be adequate to explain the relapse in Case IV, it seems inadequate to explain the remission which followed the relapse during the continuous administration of the same amount of iodine.

It is of interest to inquire whether the action of iodine in causing an underfunction of the thyroid is limited to patients who have or have had definite exophthalmic goiter. At the Mayo Clinic¹ in "several cases . . . presenting the syndrome of exophthalmic goiter and with basal metabolic rates from 0 to ± 10 " it has been observed

* In Case II the gland was definitely firmer throughout the period of iodine administration, while in Case III no thyroid tissue was palpable at any time after operation.

that the metabolism dropped 5 to 15 points after administration of iodine. No mention is made of myxedema. Strouse and Binswanger¹² could not significantly lower the basal metabolism of several patients with a "symptom complex resembling hyperthyroidism without increased metabolism" by forced iodine feeding. Martin¹³ observed a drop in basal metabolism from a normal to a subnormal level in 6 patients with simple goiter "showing symptoms of iodine deficiency." Koehler,¹⁴ referring to a group of patients with "moderate to mild hypothyroidism . . . whose untreated basal metabolic rate falls approximately between 15 to 25 per cent below normal," stated that during administration of iodides many were made worse "both from a standpoint of lowered basal metabolic rate and symptomatology." Segall,¹⁵ Martin,¹³ Snell, Ford and Rowntree,¹⁶ Cattell,¹⁷ Strouse and Binswanger¹² and Thompson and Thompson¹⁸ did not observe any change in basal metabolism during the administration of iodine to groups of 1 to 28 normal subjects; and Liebesney¹⁹ got either no change or a rise. Kunde²⁰ found that "iodine injected intravenously in the form of potassium iodide does not reduce the basal metabolism of normal dogs." Cordonnier²¹ did not observe any change in metabolism on administering potassium iodide to normal guinea pigs. Marine, Deutch and Cipra²² have reported a temporary drop in heat production in 5 of 18 normal rabbits which were fed iodine; and Webster and Chesney²³ in all of 6 normal rabbits in which they tried its effect. Hildebrandt²⁴ noted that potassium iodide had a depressing effect on metabolism when fed to normal and to thyroidectomized rats.

Thus, a reduction in basal metabolism to a subnormal level has occasionally been produced by administering iodine to patients who have never suffered from exophthalmic goiter and to normal animals. Myxedema, however, has never been produced in them so far as we are aware. Whether or not iodine will cause a lowering of the metabolism more commonly in patients who have a normal metabolism following a subtotal thyroidectomy for exophthalmic goiter than in normal subjects can be determined only by administering it for a sufficient length of time to large series of both types of individuals. It might be expected that an abnormal gland would show this response more commonly than a normal one. Whether the remnant of thyroid gland becomes normal when the basal metabolism returns to normal after a subtotal thyroidectomy for exophthalmic goiter, or whether the disease persists in it, is a matter of conjecture. Another possibility is that the small amount of gland tissue now left at operation in many clinics (2 to 4 gm., on each side) may render the patient more susceptible to myxedema than the larger amount of tissue in normal glands. In Case II iodine was given three times preoperatively and produced a subnormal metabolism (-15) only once. Postoperatively, when there was no palpable thyroid tissue, the depression was more marked and the clinical evidence in favor of

myxedema much more definite. In Case I there was only a small amount of palpable tissue after operation, and in Case III there was none. In Case IV, no surgery was done, and the patient had a fairly large goiter. In this instance the clinical evidence of thyroid underfunction was least satisfactory. Smith, Clute and Strieder²⁵ think postoperative myxedema has been more common at the Lahey Clinic since they have been doing more extensive thyroidectomies and using iodine postoperatively. A similar opinion is expressed by Graham.²⁶ The amount of thyroid tissue present thus may be a factor in determining whether or not myxedema will develop when iodine is given. While we have not made a systematic study of the subject, it is of interest that of 54 patients with a normal basal metabolism following a subtotal thyroidectomy, to whom we have given iodine, in 18 a reduction to a subnormal level occurred, but in only 3 definite or even mild myxedema.

The rate with which iodine produced definite myxedema in our cases was very slow (three to four months in Case I and in Case II after operation), yet was about the same as the rate at which a comparable degree of hypothyroidism recurs following a single intravenous injection of 10 mg. of thyroxine into a patient with typical spontaneous myxedema.²⁷ Moreover, the rate with which iodine reduces the high basal metabolism of exophthalmic goiter from a level of +40 to normal (approximately seven to ten days) is about the same as the rate with which the basal metabolism drops from a similar high level to normal when thyroid is omitted in an initially nontoxic patient who has received an overdosage. (See Figs. 6 and 3 in articles by Segall and Means²⁸ and Starr, Segall and Means²⁹ respectively, part of the data being on the patient of Aub and Stern.³⁰) These similarities in themselves suggest that it is a normal and not an abnormal hormone, the secretion of which is reduced by iodine.

While the speed with which iodine causes a normal basal metabolic rate of a postoperative case of exophthalmic goiter to drop to a low level in association with the development of myxedema is usually much less than that with which it causes a reduction in the high metabolism of a typical untreated case of the disease, there is no good reason to suppose that the mechanism in the two is different. There would appear to be merely an upward shift in the scale of metabolism throughout. This is upheld by the data on Case IV and Case II. In Case IV at one time the basal metabolism fell from +32 to -20 (52 points) on iodine; and in Case II before operation it fell from +26 to -15 (41 points). That portion of the drop which was from the normal to the subnormal level was evidently just a continuation of, and of the same nature as that portion of the drop which was from the high to the normal level.

The contrast in the frequency and generally in the speed with which iodine depresses the basal metabolism in exophthalmic goiter

when starting at a high level as compared with the relative rarity and slowness with which it depresses it when starting at a normal level after operation, is probably just an example of the general rule that in most biologic reactions it is more difficult to initiate a change from a normal to an abnormal state than a change from an abnormal to a normal one. An analogy lies in the action of thyroxin. In a patient with myxedema, the magnitude and duration of the effect of 10 mg. is much less if it is injected when the metabolism is maintained at a normal level by desiccated thyroid than if it is injected when the metabolism is low.²⁷

From the standpoint of routine clinical treatment, any patient with exophthalmic goiter who develops myxedema during the post-operative administration of iodine need not be treated with desiccated thyroid unless the myxedema persists when iodine medication is stopped.

Summary. The data presented in this and in a previous paper,³ on the rôle of iodine in the production of low basal metabolism following exophthalmic goiter, may be summarized here.

During the administration of iodine to a patient whose basal metabolism is standard normal following a subtotal thyroidectomy for exophthalmic goiter, any one of the following effects may be noted:

1. No response—the most common result.
2. Depression of the basal metabolism to a subnormal level without any accompanying clinical evidence of underfunction of the thyroid gland.
3. Depression of the basal metabolism to a subnormal level, in association with the development of myxedema, as exemplified by cases described in this article.

The latter two types of response are occasionally seen in mild untreated cases of exophthalmic goiter.

The third type of response is rare, and in this Clinic has been noted in only 3 cases following operation and in only 2 preceding operation.

In the patients reported in this paper, 1.5 to 4.5 months elapsed from the time iodine was started until the basal metabolism dropped from a standard normal level to its lowest point and myxedema developed.

The myxedema could be made to disappear either by omitting iodine or by continuing iodine and giving thyroid in addition. Both procedures produced the same clinical picture.

The development of myxedema during iodine administration is not confined to the immediate postoperative period, but may occur years after operation.

The patients who developed myxedema following operation appeared to be in a healthy state when their basal metabolism was normal and they were not receiving iodine.

Conclusions. So far as can be determined clinically, the myxedema which occasionally develops during the administration of iodine to patients who have a normal basal metabolic rate following a subtotal thyroidectomy for exophthalmic goiter, is due to an inhibition of the secretion of the normal thyroid hormone.

This suggests that iodine may cause a reduction in the high basal metabolism of exophthalmic goiter in the same manner.

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PROGRESSIVE LIPODYSTROPHY APPEARING AT MENOPAUSE.

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PROGRESSIVE lipodystrophy as a clinical entity is not new to medical literature, as about 84 cases have been reported since 1906. The clinical variations in the particular case which we have observed offer an opportunity for some interesting speculation, particularly as to the time and mode of onset and the possible relationship of etiology to certain endocrine changes.

Barraquer,^{2,34} of Barcelona, in 1906, published the first recognized account of a case of lipodystrophy, although a case had probably been previously observed by Morgagni³⁹ and another by Osler (1895). The description of a typical case as observed by the earlier writers reveals the fact that the disease is principally one of signs rather than symptoms. It begins usually in the first and second decade and is characterized by a striking loss of subcutaneous fat over the upper part of the body down to about the level of the umbilicus, while the fat below that level is either normally retained or markedly increased. In 1907 Campbell² showed before the Clinical Society of London a true case in a woman, aged twenty-two years, and in 1909 Pic and Gardere² reported a case which was typical in all respects except for exaggerated tendon reflexes. The term "progressive lipodystrophy" was used first by Simons² in 1911.

Five rather complete reviews have appeared in the literature, the most extensive being that of Reuben, Zamkin and Fox,²⁴ which was published in 1924 and contained a résumé of 60 cases. Ziegler⁴³ recently published the largest series of cases observed by a single individual, and in so doing he made some interesting observations on the sugar metabolism and mental state in this disease. Christiansen⁶ claims to have observed in the course of ten years 15 cases, but to our knowledge has reported but 4 of these.

Practically nothing is known of the etiology of this disease, although many theories have been advanced by various writers. The disease is not confined to any particular race, although several writers have suggested its predominance in Hebrews. A review of the literature does not confirm the opinion. No one lays any stress on heredity as having any significance in the etiology. However, our patient's family history would strongly suggest the possibility of an hereditary disturbance of fat metabolism. Her mother weighed over 200 pounds, and a brother, a sister, a half sister and a half brother are all extremely obese and have been so since childhood. Two of her sons and a daughter are overweight. The daughter, who was unusually fat as a child, has recently been married and is gradually becoming still more obese. Zalla,⁴⁰ Marañón and Soler²⁰ suggest that "lipodystrophy is nothing more than an extremely accentuated form of distribution of adipose tissue and, therefore, not uncommon. In consequence, there is a whole series of gradations of intermediate forms between the accentuated cases and the normal state." Excessive fat of the buttocks, "steatopygia," is seen as a normal development in the female of certain African races. Gesell¹¹ has recently reported 2 cases of hemihypertrophy in children and "interprets the condition to be an atypical or a paradoxical form of twinning." Considering a disturbance in fat metabolism as the possible etiology of the disease, Mirallié and Fortineau²² tried high-caloric diets with no gain of fat in the atrophic areas. Sprunt³⁰ was more successful with the same type of diet, but, in addition, he used pituitary gland and sodium cacodylate.

Boissonnas² expressed the unique theory that the atrophy above the waist line was pathologic while the hypertrophy below represented an attempt at compensation present in the whole body but effective only in that area. There is certainly some alteration in fat metabolism in cases of "intestinal lipodystrophy" as reported by Whipple,³⁷ Blumgart and Tucker.³²

Whipple³⁷ applied the term to an unusual case he reported in 1907, which was characterized by a progressive loss of weight and strength, indefinite abdominal and arthritic pains, and associated with frequent stools containing large quantities of neutral fats and fatty acids. Only 1 of the 5 cases reported has come to necropsy. The pathologic findings were enlarged intestinal villi, lymph spaces filled with large masses of neutral fats and fatty acids, and an

infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells.

Infection or the toxic effect of an infection producing organic changes in the brain has been proposed as a theory to explain the remote changes found in the distribution of fat elsewhere in the body. As will be mentioned later, the neuropathology concerning this particular disease is still far from being definitely established. It might be mentioned that Wartenberg³³ has suggested the possibility of an "encephalitic" infection or toxin involving an area in the region of the brain stem, mesencephalon or third ventricle.

The endocrines offer a field for interesting speculation in this disease, as with many other metabolic disturbances. In 3 of Ziegler's cases, the metabolic rate was high, and in 1 of these cases there were recurring attacks of exophthalmic goiter. A series of 7 cases showing disturbances of the thyroid was reported by Maranon and Soler.²⁰ Many writers, including Klein,^{12,28} Christiansen⁵ and Marburg,²¹ have believed the syndrome to be a combination of endocrine and neurotrophic disturbances. One of Klein's patients responded to treatment by pituitary extract. Sprunt³⁰ reported similar results, but, in addition, gave a high-caloric diet. A question of involvement of the pineal gland was raised by Kelin,^{7,25} who suggested that excessive localized atrophy of the gland at its involution (at age of six, which is age of usual onset of lipodystrophy) produces irregular function of the gland and consequent disappearance of fat in certain areas, the increase in fat below the waist being a secondary sexual characteristic of puberty. But, as Watson and Ritchie point out, the pineal syndrome of excessive height, general adiposity, hypertrichosis, somnolence and sexual precocity is not seen in lipodystrophy.

To support the theory of pituitary disturbance in this disease, one naturally associates the well-known syndromes, such as Frölich's and Lorain-Levi and also the numerous metabolic disturbances which are due to pituitary dystrophies. In reviewing our cases of pituitary disease, we selected one, a Lorain-Levi type, which we believed showed some relationship to the case in question. A brief description will illustrate our point.

Case Abstract of Lorain-Levi Syndrome. The patient was sent to the clinic because of amenorrhea. Family history was entirely negative. Her past health was good, except that she had had the usual exanthems of childhood. Recently she had an epiphyseal separation of the right femur at its proximal end. Roentgenograms at that time showed all epiphyseal lines still open in hands and feet. On examination, we found a fairly well-nourished girl, aged twenty years, lacking all secondary sexual characteristics and having infantile pelvic organs. The lack of adipose tissue and bony development gave her the appearance of a slender preadolescent male (Fig. 1). Roentgen ray findings confirmed clinic suspicions as the films of the head showed a marked enlargement of the sella turcica (Fig. 3) with several calcified areas and the skull was somewhat thin. There was a moderate widening of the suture lines, suggesting an increased intracranial pressure.

We have, therefore, a case of the Lorain-Levi type (preadolescent hypoactivity of the anterior lobe) of pituitary disturbance giving us much the same picture that we see in the upper part of the body in a case of progressive lipodystrophy.

Frazier,⁴⁵ in his recent review of 15 cases of pituitary cachexia (Simmonds' disease) has shown that there may be an extreme emaciation of the trunk and extremities. The emaciation, or total lack of adipose tissue, in the trunk and upper extremities in pituitary cachexia, Lorain-Levi syndrome, and progressive lipodystrophy is decidedly similar, so the idea that there may be a pituitary disturbance in the latter disease is not so remote. Of course, the entire question of the causal factor in lipodystrophy is in the realm of theory and no one knows which factor may be of the most importance.

Neurotrophic disturbances have been mentioned more frequently in discussions as to etiology than any other factor. One can readily surmise that the discussion of the trophic nerves or neurotrophic centers is still in the field of hypothetical consideration, and that it leads one into much speculation concerning the association of neurotrophic and endocrine factors as a combined cause of the disease. Trophoneurosis, perhaps due to abnormal innervation, has been suggested by Rominger.²⁷

The segmental arrangement of the disease in some cases has pointed toward the basal ganglia as being the site of the involvement. The disturbance in fat distribution in the lower part of the body closely resembles, though highly exaggerated in some cases, that of women at the menopause, and the possibility is not so remote that this disturbance may be due to an endocrine dystrophy, while that of the upper part of the body is due to a neurotrophic disturbance. Klein^{12,28,43} believes that all the signs in this disease are due to disturbances of the glands of internal secretion and of the sympathetic nervous system and that a subthamic vegetative center plays the most important rôle. He thinks the center must be regarded as "localizatory differentiated," because only the upper part of the body becomes emaciated. The accumulation of fat in the lower part remains unexplained. Since lipodystrophy usually affects females during puberty, Klein¹² believes it is connected with the maturing of the ovaries. Wolff and Ehrenclou³⁸ also consider the disturbance as possibly due to a general imbalance caused by pathologic change in trophic centers at higher levels.

The pathologic findings from biopsies performed by Simons,² Christiansen,⁶ Feer¹⁰ and Smith²⁹ were uniformly the same. The epidermis and dermis were found to be normal; the one histologic change observed in all cases was the practically complete absence of fat in the subcutaneous tissue. No microscopic changes were found in underlying muscles. Necropsies are also reported by Husler, Sarbo, and Weber and Gunewardene.³⁵ The latter observ-

ers report a case of a girl, aged thirteen years, who died of pyemia following a left mastoid operation. Microscopic examination of glands, one ovary, pituitary and both suprarenals showed no unusual findings. There was an abnormal amount of colloid in the acini of the thyroid gland, and there was more than the normal amount of interstitial tissue present. Sections from various parts of the gland suggest that there was a moderate degree of oversecretion of colloid which was associated with a slight fibrosis and actual diminution in the size of the gland. Histologically, there was no fatty tissue present in the scalp or upper abdominal wall. Consistent pathologic findings which would have any bearing whatsoever on the etiology have not been found. For instance, Sarbo reports a case showing a lesion in the corpus striatum, while Zalla reports another of a pituitary cyst. Sprunt shows one case having a persistent thymus and still another with atrophy of the thymus. A detailed pathologic report of brain findings is contained in the article by Otto Marburg, but the value of his observations is depreciated by the fact that the patient died of a purulent septicemia.

The symptomatology in this disease is indeed meager, since practically the only complaint is weakness. Ziegler,⁴² in his recent review of 82 cases, gives particular attention to the "neuropsychiatric aspects of lipodystrophic disturbances." He states that in 15 cases there was a marked self-consciousness; in 17 cases the family or friends were worried about the patient's health; in 8 cases nervous and mental symptoms were rather prominent; in 43 cases no abnormality of behavior was noted. Our patient has never shown any neuropsychiatric symptoms.

Treatment. No form of method of treatment has as yet been found to be of particular value. Of the glandular preparations, whole pituitary has been beneficial to some patients complaining of weakness. Ziegler⁴³ has reported some success with ovarian extract. Two cases, both women, reported by Boston,³ in 1923, showed some improvement under treatment. The treatment in each case consisted of three capsules daily containing small doses of cerebrin, strychnin sulphate, parathyroid, whole pituitary and potassium citrate. Case 1, a woman, aged thirty-one years, took the capsules daily for fourteen months and gained 17 pounds. Case 2, a girl, aged sixteen years, followed treatment for a shorter period and gained 7 pounds. The experience of Mirallié and Fortineau²² with rest and high-caloric diets has not been encouraging. Sprunt,³⁰ however, reports success in one case with rest and forced feeding. This form of treatment should be tried. Protracted administration of insulin was tried by Rominger with negative results. The body weight did not increase, there being only a further accumulation of fat in the lower parts of the body. No writer has ever been able to cause any change in the facial condition other than by subcutaneous injections of paraffin, which have been of questionable value.

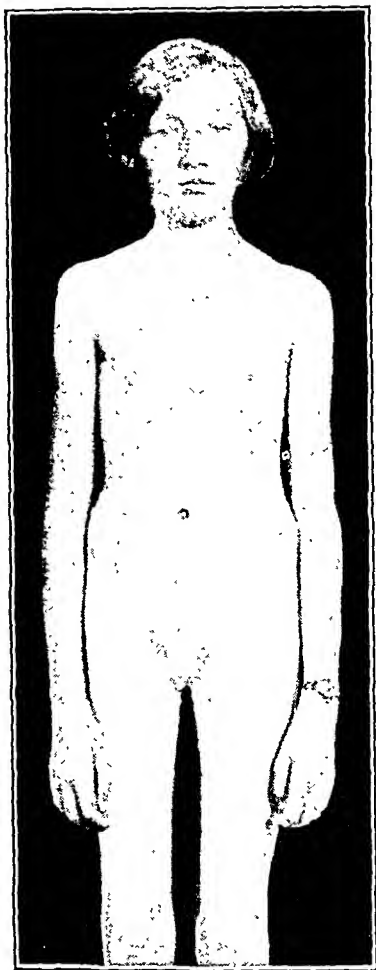


FIG. 1. — Case I. Girl, aged twenty years, showing lack of adipose tissue, bony development and secondary sexual characteristics.

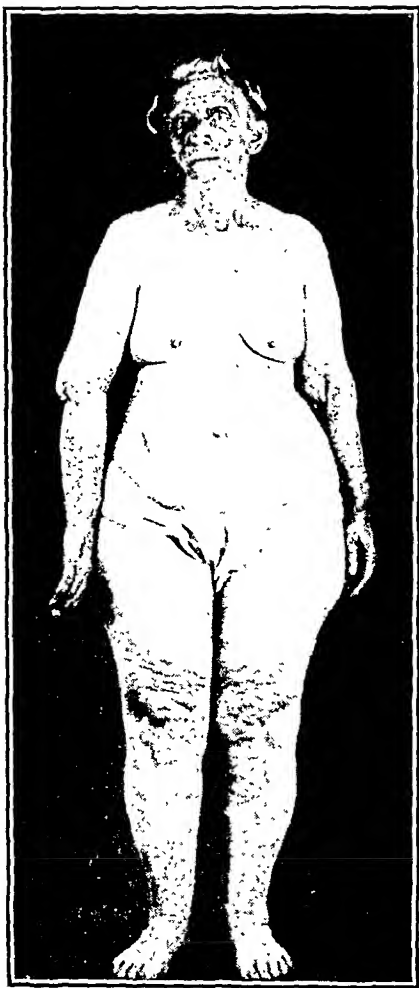


FIG. 2.—Case II. Fat pad shown on right elbow. Note lack of fat in face and chest, with an increase below the waist.

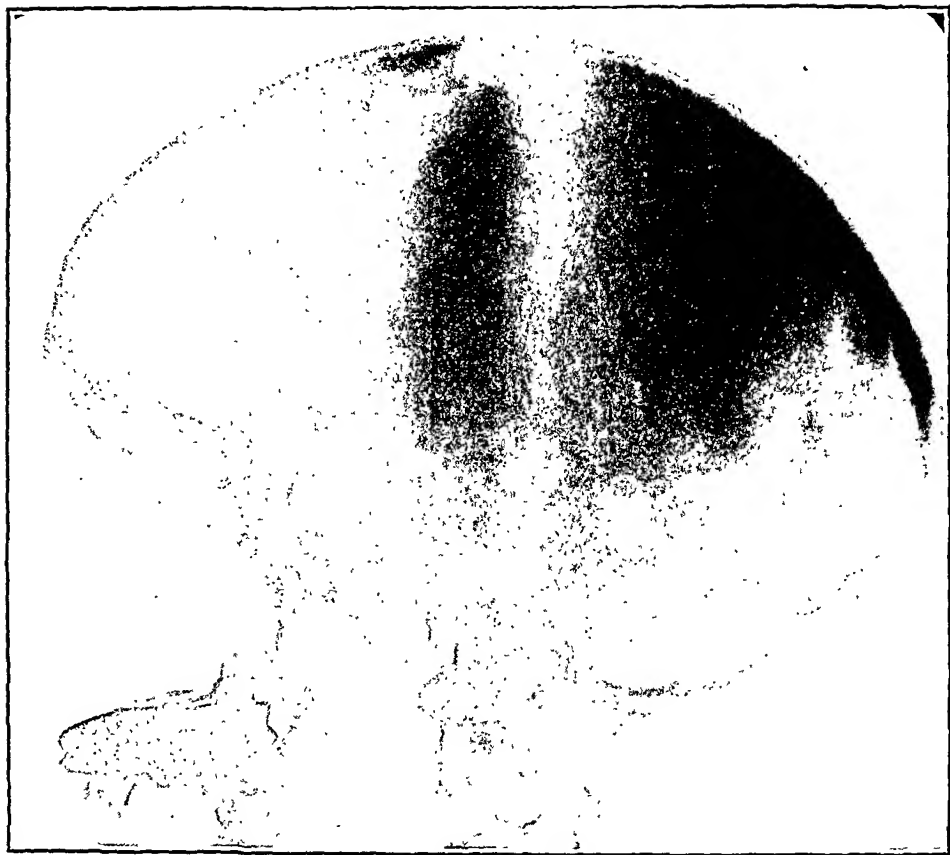


FIG. 3.—Case I. Note enlarged sella with calcified areas.



FIG. 4.—Case II. Appearance of patient at the age of twenty-five years.



FIG. 5.—Case II. Cadaveric expression due to loss of subcutaneous tissue.

Case Report of Lipodystrophy. Mrs. M. H., aged sixty-five years, housewife, came into the clinic complaining of a loss of fat in both sides of the face and an increase in fat about the hips and thighs.

Family History. The patient has a brother, sister, half brother and half sister who are obese, and have been so since childhood. Her maternal aunts and uncles have all weighed over 200 pounds.

Past History. Other than the usual exanthems of childhood, she had typhoid fever at the age of seven years. Asthma has been disturbing to her since the age of twenty-five years. It is worse in damp weather.

Menstrual History. Her periods began at the age of eleven years, and they ceased at thirty-nine years; otherwise they were normal.

Marital History. The patient was married at twenty-five years (Fig. 4). She states that at that time she had small breasts. She gave birth to five children, four sons and one daughter. The first and fourth sons weigh over 180 pounds. The third son has goiter and the second son has idiopathic epilepsy, which began at twenty-four years. The latter, whom we shall mention later, has total blood lipoids of 333 mg. per 100 cc. (normal, 200 mg. per 100 cc.) and a cholesterolemia of 221 mg. per 100 cc. (normal, 140 to 170 mg. per 100 cc.).

Present Illness. After the age of forty years (menopause) she began to rapidly take on the fat in the arms, lower abdomen and legs. The increase of tissue below the umbilicus and the decrease above made it impossible for her to use a shopmade dress. In the spring of 1928 (age of sixty-four years) she reached her greatest weight of 203 pounds, due to the increase in fat about the hips and thighs, while the face took on a cadaveric expression (Fig. 5). At about the same time she noted a gradual decrease in the fat of the arms except for fat pads which remained at the elbows (Fig. 2).

Examination. General: The patient's weight is 176 pounds, and she is 63½ inches tall. She appears about her actual age. Her hair is gray. The face shows the typical loss of subcutaneous fat. The skin of her hands is dry and shiny; that of her arms, particularly the upper arms, is flabby. The skin over the upper arms can be raised several centimeters; definite fat pads can be seen over the elbows. The thorax and upper abdomen, down to the umbilicus, are rather thin. The breasts are flattened and contain little fat or glandular tissue.

Vision: Right, 6/30—; left, 6/30—. Pupillary reflexes are normal. Arcus senilis is present in both eyes. Fields are normal, and fundi are negative with the exception of marked sclerosis of the vessels.

Oral cavity: There are complete upper and lower dentures. The throat shows chronic injection over both anterior pillars. The tonsils show moderate fibrosis with few crypts and follicles. There is no free pus, but a mild chronic injection over the pharynx. Few enlarged cervical glands—tonsillar glands—are palpable. Aside from a small shelf along both floors, the nose is negative. The ears are negative, and the sinuses, clear.

Heart: Rate is 64. Rate and rhythm are regular. Sounds are normal and there are no murmurs. Blood pressure is 170 systolic and 90 diastolic. No cardiac enlargement is present. The lungs are normal to inspection, palpation, percussion and auscultation. Liver and spleen are not palpable. No tumor masses nor tender areas are found in the abdomen.

Neurologic examination: Her gait and station are normal with eyes opened or closed. She has an interesting, unusual padding of fat over the elbows. There are no tremors of the hands on extension. She has a radial deviation of the terminal joint of both forefingers. There is no intention tremor, no ataxia, no astereognosis, no adiadokokinesis. The patient states that when she was younger she had a marked laxity of the elbow joints. This is still present to a certain extent.

Cranial nerves: She has no facial paralysis. There is apparently considerable atrophy of the lower facial group of muscles, but there is no loss of motor ability. She moves the jaws, closes the eyes normally. The palate moves normally. The tongue is quite smooth in appearance. The extraocular movements are normal. The consensual reflex is normal. There is no nystagmus.

The deep reflexes are normal. There is no Babinski and no clonus. She has varicose veins in the right leg. Her toe nails are unusually dry and hard. There is a tendency toward marked convexity of the nails, especially of the great toe on each foot.

Sensation: Vibration, pain, light touch, motion and position, and deep pressure are all normal.

Laboratory Findings. These include: Urine: Light yellow, clear; negative for albumin, glucose, indican and casts; few red blood cells; many white blood cells and vaginal epithelial cells. Blood count: Hemoglobin, 85 per cent; red blood cells, 3,650,000; white blood cells, 4650. Differential count: Lymphocytes, small, 43; transitionals (endotheliocytes), 4; polymorphonuclears (neutrophils), 51; eosinophils, 0; basophils, 2. The Kahn test was negative. Total lipoids: 298 mg. per 100 cc. (normal, 200 mg. per 100 cc.). Cholesterol: 229 mg. per 100 cc. (normal, 140 to 170 mg. per 100 cc.).

Roentgen-ray Findings. Films of the head are negative. The sella turcica is of normal size and without bone erosion.

Comment. Although our case has contributed several interesting points, it has added nothing toward the solution of the etiology of the disease. Examination of the photographs will convince the reader that the case presented is a typical progressive lipodystrophy, closely resembling Case 2 of Ziegler's recent series, with the exception that our case presents fat pads at the elbows which have the appearance and feeling of small lipomas. Bavonneix cited a case in 1923 with similar pads.

Our case is unusual in that the disease did not make its appearance until after the menopause, and perhaps some speculation could be offered as to the question of this being an ovarian or an ovarian-pituitary dystrophy. She always had small breasts, and never took on weight above the umbilicus except in the arms. The loss of fat above the level of the umbilicus suggests the possible association of this disease with pituitary cachexia and also with Lorain-Levi type of pituitary dystrophy.

Our patient has had asthma which dates from the time of marriage and we know of no other case reported to have a like complication. Perhaps the most common complications reported are diabetes mellitus and hyperthyroidism. Nervous and mental symptoms have never disturbed her, and she has had none of the usual signs of weakness and fatigue.

The few blood chemistry findings reported by other writers show no abnormalities. Fear even tried to produce a lipemia by administering 200 gm. of 20 per cent cream by mouth, but failed. Our case shows both a high-cholesterol and high-total lipid blood content, as is also true of her son who has epilepsy. Whether or not

these chemical findings are of any significance, we are at present unable to say. Her family history suggests the possibility of an hereditary disturbance in fat metabolism.

Summary. 1. A case of progressive lipodystrophy appearing after the menopause is presented.

2. A case of Lorain-Levi type of pituitary dystrophy is cited to show a possible association of endocrinopathy and progressive lipodystrophy.

3. A high cholesterol and total lipid content in the blood of both the patient and her son suggests the possibility of a familial disturbance in fat metabolism. However, we would hesitate to say it has any significance as regards the etiology of the disease.

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PROGRESSIVE LIPODYSTROPHY OF THE LOWER EXTREMITIES.

REPORT OF A CASE.

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IN view of the full discussion of this rather rare and interesting condition by Currier and Davis in this issue, I am briefly reporting this case because of two features unusual in this group of patients. The lipodystrophy appears at or about the menopause, and shows a reversed distribution of the fatty changes. Sprunt, in describing the condition, says that "It is characterized by a remarkably complete disappearance of the subcutaneous fat of the face, of the neck and usually of the arms and upper portion of the trunk. This emaciation begins, as a rule, in childhood, first involves the face and then the lower parts progressively from above downward. Simultaneously or beginning a few years later there is an excessive deposit of subcutaneous fat on the lower portion of the trunk and on the legs, which may be in grotesque contrast with the emaciation above the waist."

Case Report. Mrs. M. O., aged fifty-five years, first consulted me in January, 1930, complaining of pain under and between the shoulders and loss of weight. She reported that she had diabetes and high blood pressure.

Family History. Native, white, American stock. Mother and two uncles died of Bright's disease. Several brothers and sisters are quite well and of average size and weight. There is no record of a similar condition in her family.

Past History. Since childhood, no illnesses except tonsillitis and influenza in 1928. Tonsils were removed in 1928.

Marital History. The patient has been married three times. The first when she was twenty years of age. There was one child and after three years her husband died of tuberculosis. The second marriage resulted in the birth of four healthy children. There were other pregnancies, twice with twins, all of whom were lost and once a premature birth which died. Her third marriage was only five years ago. The menopause was complete at fifty years.

Present Illness. The patient's legs began to lose all superficial fat and their former shape about three years ago. Two years ago this loss seemed complete, and since that time there has been no further change in their appearance. The patient had been through a rather exhausting nervous strain just before this. Immediately after the menopause she lost her father with pneumonia. Her mother was a semi-invalid and her care was trying. It was during this time that she first noticed the "wasting away" of her legs and she worried a great deal about their appearance.

Following an attack of influenza in 1928 she has suffered with pains between the shoulders, which she describes as feeling like a great many sharp knives sticking under her shoulders. There is also numbness in both arms at times. Two years ago she consulted a physician who found a rather high blood pressure and sugar in several specimens of urine. She was given diet instructions and advised to have her tonsils removed. After tonsillectomy the pains and numbness were better, and pains that had been present in the lower extremities disappeared. She states positively that at this time there was absolutely no fat present over the lower extremities.

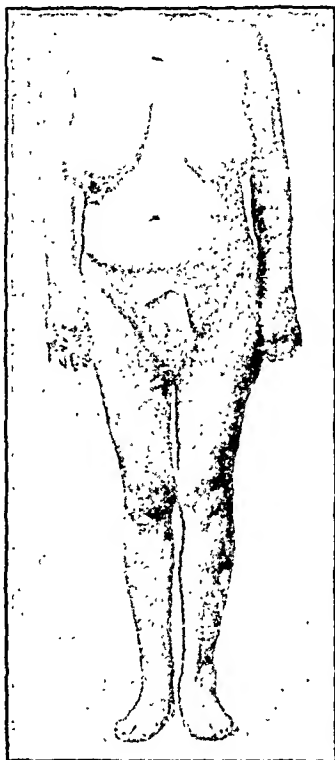
Physical Examination. The patient's lower body presents a striking contrast to the upper portion. The hips, thighs and legs are so slender that they might have well belonged to another person. (Note photograph.) The arms, neck, chest, abdomen and breasts are well covered with subcutaneous fat. From the level of the waist down there is absolutely no palpable subcutaneous fat. The contour of the muscles of the thigh and leg are clearly discernible, the legs appearing quite masculine. The hips and gluteal regions are remarkably thin and flat when compared to the abdomen and shoulders above. The loss of fat is bilaterally symmetrical. It is just the reverse of the usual distribution in the cases of lipodystrophy heretofore reported.

The essential findings on physical examination were important. There were no demonstrable neurologic changes. All deep and superficial reflexes were present normally on both sides in the upper and lower extremities. There were no Romberg or Babinski signs, no clonus, no sensory changes to touch, pain or temperature at any point. There was no muscle weakness, no interference with locomotion and, in short, nothing to indicate an organic neurologic basis for the condition, except the symmetrical deformity and the abrupt level of change in the distribution of subcutaneous fat.

The patient's weight is 138 pounds; height, 64 inches. Her average weight had been until this last year, 155 pounds. The loss of 15 pounds she attributed to diet efforts to control glycosuria.

Vision shows slight error, readily corrected. Pupils equal, active to light and in accommodation. Ophthalmoscopic inspection shows normal fundi except for slight sclerosis. Diseased tonsils and teeth had been removed. The thyroid was not enlarged and there were no evidences of

disturbed thyroid secretion. No enlarged glands in the cervical triangles, either axilla, about the elbows or in either groin. The breasts are large, flabby and pendulous.



Mrs. M. O., lipodystrophy of lower extremities.

The heart is slightly enlarged to the left. No murmurs, no accentuations, regular rhythm, rate 86 to 90. The radials and brachials are palpable and slightly thickened. Fluoroscopic examination of the chest and heart shows a slight increase in heart size and some widening of the aortic arch. The lung fields are clear. The blood pressure is 165 systolic and 90 diastolic.

The abdomen is relaxed; no masses; no areas of soreness. Vaginal examination negative, except for some relaxation of the outlet and an old cervical tear. Rectal examination shows small external hemorrhoids.

Laboratory Findings. Urines (three specimens) all showed traces of albumin, sugar in fairly large amounts, no acetone and microscopically only an occasional hyaline cast. Hemoglobin, 85 per cent (Dare); red blood cells, 4,350,000; white blood cells, 6750. Differential count: Polymorphonuclears, 54 per cent; lymphocytes, 35 per cent; mononuclears, 5 per cent; eosinophils, 6 per cent. No plasmodia found. Blood Wassermann test negative. Kahn negative. Spinal Wassermann test negative. Blood sugar: Fasting, 181 mg. per cent; two hours p.c., 285 mg. per cent. Feces: No ova or parasites found. Basal metabolic rate, -7.

Radiograph of the sella turcica: Normal in size and contour.

Summary. A case of progressive lipodystrophy with two unusual features is reported.

1. The lipodystrophy involves the lower extremities rather than the upper body as heretofore reported cases have done.

2. The lipodystrophy first appeared in this case after the menopause.

NONDIABETIC GLYCOSURIAS.*†

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IN a series of previous communications^{1,2,3,4,5,6} one of us has reported the results of studies on various aspects of the metabolism of galactose in health and disease and described the technique of a tolerance test based upon its use. The present report deals with a study of patients who have demonstrated a spontaneous glycosuria without direct evidence of diabetes and presenting a variety of disease conditions not intrinsically associated with the pancreas. Before discussing the methods adopted and the results obtained, a few words of definition are necessary.

The term "diabetes" is gradually being delimited to that disturbance of the carbohydrate metabolism produced by a deficiency of insulin, the product of the endocrin activity of the islands of Langerhans. Glycosuria is but one evidence of the condition and one not wholly indicative, as both the treated diabetic can be rendered sugar free and various artificial agents can produce it. Hyperglycemic blood-sugar levels offer much more certain evidence of the presence of the disease, yet even here the occasional observation of an insulin-resistant patient raises the question of a possible second mechanism. The antagonistic action to insulin of the extract of the posterior lobe of the pituitary has been demonstrated by several,⁷ but in a patient studied by the author and recently reported by a colleague,⁸ an insulin-resistant hyperglycemia developed after the surgical removal of the posterior hypophysis, the latter fact being verified at autopsy. Further, the enormously increased tolerance for carbohydrate exhibited by the severe case of pituitary failure with a completely normal blood sugar offers yet another stumbling block to a theory of causation that involves insulin activity alone. The term diabetes will be confined in this paper to that disease entity which is traceable directly to a condition of lowered endocrin function of the islands of Langerhans. The warrant for such position is supported by ample authority.⁹ That insulin *qua* insulin may be involved in the mechanism of some of the other glycosurias is conceded. Equally, true pancreatic diabetes may and does coëxist with other endocrin and nonendocrin

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conditions which in themselves are capable of causing glycosuria. The terms "renal" glycosuria, "benign" glycosuria and others have been applied to those conditions in which there is a common finding of sugar in the urine but no other evidence of functional or organic disease of the pancreas. In these states the common end result is more than compensated by a variety of clinical and laboratory evidence wholly at variance with those features produced by known pancreatic disease.

The subject is a large one, the literature, both polemical and recording, vast and no attempt may be made here to do more than offer certain objective evidences which bear on the problem. The title of this paper defines a position only and is hoped to be sufficiently broad to be inclusive. The present statement is frankly preliminary in character. The questions involved are of major import and the whole field characterized by many contradictory opinions and interpretations, each of which, however, is able to marshal an impressive array of evidence felt by some to be supporting. It is intended that the facts here recorded may make some contribution to the ultimate resolution of certain of the problems involved. No attempt is made to review the extensive literature, the few citations given being expository to the text and included solely for that reason. This explains what would otherwise be an overfrequent reference to the senior author's publications.

This study draws its material from a consecutive series of nearly 2000 patients referred for diagnostic investigation. While all presented initially some evidence of possible endocrin disorder, both the absence of glandular disease and an underlying nonendocrin disturbance was demonstrated in more than one-third of the series. The methods of investigation have been described in some detail elsewhere.¹⁰ Briefly, it may be stated that each patient received an intensive clinical and laboratory study, and the facts thus elicited were interpreted in terms based upon the previous study both of a long series of normal controls and a similar group of established endocrinopathies. The various facts were interpreted in terms of ductless glandular disease only after a possible causative nonendocrin condition had been eliminated by test and observation. Finally, the differentiation of the several glandular conditions from one another depended on a similar analysis of the evidence¹¹ and comparison and contrast with established criteria.

Age. In the majority of cases the age at which the patient is referred for diagnostic study is not that of the onset of the condition. Further, consideration of the latter is not more helpful, as patients will frequently date the beginning of a condition from some outstanding event in their medical history which actually has nothing to do with the real difficulty. In series of sufficient length these factors should be compensatory and so the relative figures assume meaning. Review of the age groupings for the entire series and

for that portion showing glycosuria, demonstrates no significant differences and thus eliminates an age element.

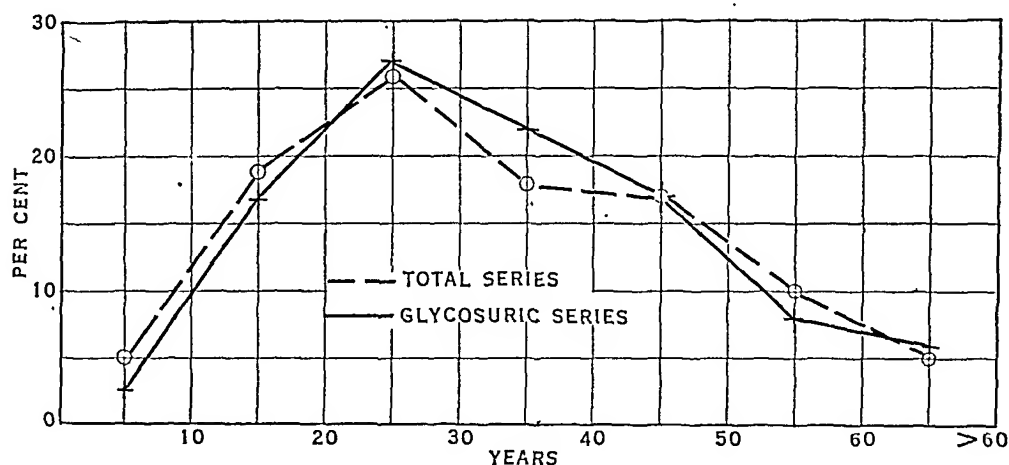


CHART I.—Comparison of age incidence in cases with glycosuria and those of the complete series from which the former are drawn.

Sex. The possibility of a sex influence can be resolved in the same way. The data are given in Table I.

TABLE I.—SEX PROPORTION IN CASES WITH GLYCOSURIA.

Group.	Number, total.	Females.		Incidence in complete series, per cent.
		No.	Per cent.	
Nonendocrin	80	43	54	63
Pituitary	103	63	62	60
Thyroid	46	31	67	73
Gonad	47	47	100	95
Adrenal	6	4	67	67
Pluriglandular	4	4	100	97

The correlations in all but the nonendocrin and thyroid groups give no support to a possibility of sex influence. The gonad figures are but one more evidence of the absence of any testicular influence upon carbohydrate metabolism¹² in adult years at least. In the nonendocrin group a possible sex element is apparent, and this suggestion receives some support from the fact, to be noted later, that many of the thyroid cases show nonendocrin complications which are themselves associated with glycosuria. If the group be taken as a whole the differences are not striking (2.5 per cent), and a male influence, if present, is not of large magnitude nor is it operative in the endocrin group.

As the present survey is designed solely to trace possible influences in the production of glycosuria, the group presenting evidences of disease of a nonendocrin character first claims attention. Any of these conditions may occur as complications in the endocrin group, while naturally, on the present basis of classification, the converse cannot obtain. Certain essential data from the former series have been collected into tabular form. The etiologic designation of each

case is based upon that condition presented by the patient which was considered to be of primary importance. Secondary complications will be considered later.

TABLE II.—APPEARANCE OF GLYCOSURIA IN THE NONENDOCRIN DISEASE GROUP.

Group.	Subgroup.	No., total.	Glycosuria.		
			No.	Per cent.	Group, per cent.
Infections	Tuberculosis	40	1	2.5	3.4
	Arthritis	36	1	2.8	
	Focal infection	43	2	4.7	
Mental and nervous diseases	Neuroses	52	1	1.9	5.5
	Psychoneuroses	40	2	5.0	
	Psychoses	18	3	16.7	
	Central lesions	64	18	28.1	
Disorders of nervous system	Epilepsy	24	1	4.2	18.3
	Parkinsonian syndrome	17	2	11.8	
	Mental retard.	15	1	6.7	
Metabolism . . .	Malnutrition	26	2	7.7	7.7
Disorders of cardiovascular system	Cardiac	47	4	8.5	5.3
	Renal	43	2	4.7	
	Cardiorenal	43	1	2.3	
Blood diseases	Primary anemia	11	2	18.2	19.0
	Leukemia	10	2	20.0	
Tumors	Neoplasm, malignant	10	4	40.0	18.4
	Neoplasm, benign	6	1	16.7	
	Nontoxic goiter	22	2	9.1	
Ear diseases	68	2	2.9	2.9
Asthma	15	1	6.7	6.7
Diseases of liver	62	14	23.0	23.0
Syphilis	40	10	25.0	25.0
Normals	33	1	3.0	3.0
Totals	785	80	..	10.2

Ten per cent of a group of nearly 800 patients presenting a variety of conditions demonstrated sugar in the urine. A further inspection shows, however, that significant relative occurrence is confined to but a few of the several etiologic groups.

The psychoses, lesions of the central nervous system with the Parkinsonian cases which really belong in this category, the blood diseases, malignant neoplasms, diseases of the liver and syphilis, account for nearly 70 per cent of the total number, while the scatter of the remainder lacks any clear-cut definition. Since these several conditions appear with suggestive frequency, their occurrence as complications is pertinent in those cases initially listed under another etiologic group. These data are collected in the next table. The blood diseases and malignant neoplasms are omitted as they did not present as complications in this series.

The case with asthma in Table II is omitted as the patient was under heavy suprarenin medication, a fact potentially introducing another mechanism than that under investigation. The "normal" case was pregnant and the psychoneuroses are as suitably regarded as belonging to the psychotic as to the neurotic group.

TABLE III.—EFFECT OF COMPLICATIONS IN THE CASES WITH GLYCOSURIA IN NONENDOCRIN GROUP.

Group.	Subgroup.	Complicated.				Uncomplicated.	
		Total with glycosuria.	Central nervous system.	Liver.	Lues.	No.	Per cent.
Infections	Tuberculosis	1	0	0	0	1	2.5
	Arthritis	1	0	0	1	0	0
	Focal infection	2	0	0	0	2	4.7
Mental and nervous diseases	Neuroses	1	0	1	0	0	0
	Psychoses	3	0	0	0	3	16.7
	Central lesions	18	..	0	0	18	28.1
Disorders of nervous system	Epilepsy	1	..	0	0	1	4.2
	Parkinsonian syndr.	2	..	0	0	2	11.8
	Mental retardation	1	..	0	0	1	6.7
Metabolism . . .	Malnutrition	2	0	1	0	1	3.8
Disorders of cardiovascular system	Cardiac	4	3	0	0	1	2.1
	Renal	2	0	1	1	0	0
	Cardiorenal	1	1	0	0	0	0
Blood diseases	Primary anemia	2	0	0	0	2	18.2
	Leukemia	2	0	0	0	2	20.0
	Neoplasm, malignant	4	0	0	0	4	40.0
Tumors .	Neoplasm, benign	1	0	1	0	0	0
	Nontoxic goiter	2	0	1	0	1	4.5
Ear disease	2	0	0	0	2	2.9
Liver diseases	14	0	..	0	14	23.0
Syphilis	10	0	0	..	10	25.0

That glycosuria is associated with a variety of endocrin conditions outside of the prototype produced by pancreatic hypofunction has long been recognized and frequently recorded. A certain confusion has arisen at times through failure to recognize the possibility of changing function levels in the same disease state, although Cushing¹³ a number of years ago recorded this phenomenon with the pituitary in acromegaly.

The present endocrin series is no exception to this general rule. Following the procedure adopted for the nonendocrin material, the data have been collected in tabular form. The dysfunctional pituitary group is composed of those cases in which diagnostic study has demonstrated an underactivity of the anterior and overactivity of the posterior lobe, this being the common formula of dysfunction. The dysfunctional thyroid cases were those in which individual evidences of both hypofunction and hyperfunction were demon-

strable in the same person. A number of these were patients in whom the gland was undergoing a functional involution from an initial overactivity to a terminal underactivity. As the various objective evidences of disturbed function do not modify with uniform speed, such transitional conditions are spontaneously synthesized and constitute true dysfunctional levels.

The ovarian group were either castrates or patients with those functional failures which correspond exactly to the picture produced by the removal of the ovaries. The adrenal patients were cases of Addison's disease, proven by autopsy, or less certainly, patients with the condition designated as "hypoadrenalism." The warrant for the inclusion of the latter has been discussed elsewhere.¹⁴

The pluriglandular cases were chiefly those in whom an endocrin hypofunction produced by surgical ablation was superimposed upon a functional derangement involving a second ductless gland.

The raw data from the series are collected in Table IV.

TABLE IV.—PRIMARY ANALYSIS OF ENDOCRIN GROUP.

Gland.	Function.	No.	With glycosuria.		
			No.	Per cent.	Group, per cent.
Pituitary . . .	Hyperfunction	7	5	71.4	
	Dysfunction	367	87	23.7	
	Hypofunction	188	11	5.9	
Total	562	103	..	18.3
Thyroid	Hyperfunction	41	9	22.0	
	Dysfunction	92	16	17.4	
	Hypofunction	198	21	10.6	
Total	331	46	..	13.9
Gonad	Hypofunction	204	47	23.0	23.0
Adrenal	Hypofunction	11	6	54.5	54.5
Pluriglandular . .	Dysfunction	21	4	19.0	19.0
Grand total	1129	206	..	18.2

The number of the cases in each group is determined by the relative frequency of appearance in a consecutive series and can be considered as fairly representative. The partition of the several functional levels is not so significant as several unrelated factors influence them. The clear-cut evidences of acromegaly and exophthalmic goiter frequently render elaborate diagnostic studies unnecessary.

The percentile representation of glycosuria in the several stages of pituitary disease is striking and reflects the important part played by this gland in the regulation of one phase of the sugar metabolism. The lower incidence in the thyroid group harmonizes with the common observation of its lesser significance in sugar utilization. The seeming anomaly of glycosuria appearing with hypofunction of both the pituitary and the thyroid, conditions associated with increased assimilation limits for carbohydrate, will

be touched upon later. The figures for the other glands do no more than indicate the influence which each exercises on sugar metabolism as shown by the depression of the sugar tolerance.

The incidence of glycosuria is about the same in this group as in the important subgroups of the nonendocrin series already discussed. The large numerical contributions are from cases with pituitary dysfunction and ovarian failure, the one deriving from an overactivity, the other an underactivity of the endocrin gland involved. The highest relative frequencies are in the two small groups respectively of pituitary hyperfunction and adrenal failure. In the first the posterior lobe activity is the same in kind as in the state of dysfunction, so that a correlation is not surprising. The adrenal status parallels that of the ovary. The indication of the real influence of endocrin activity on glycosuria can best be estimated, however, when due allowance has been made for the several potentially significant nonendocrin complications.

Two of the cases with pituitary dysfunction had lesions of the central nervous system (brain tumors) and the pituitary condition was possibly only secondary to increased intracranial pressure. In addition, 4 more had well-defined psychoses, a condition also found in 1 of the cases of hypofunction.

Hepatic disease is frequently associated with functional derangement of the thyroid¹⁵ and one-third of the present hypothyroid group demonstrated this complication. In addition, 1 more liver case was found in each of the other two groups. Two more of the hypothyroid patients were pregnant and so must be omitted from consideration. Five of the ovarian cases were significantly complicated, 1 of them being the only case of syphilis in this series. One adrenal case was psychotic.

Summarizing, nearly one-eighth of the endocrin cases present nonendocrin complications to which the glycosuria might be ascribed. Further, half of these are found in the thyroid group which had initially the smallest percentage of incidence in the endocrin series.

The findings in the endocrin group after deletion of the cases presenting complication can be presented most compactly in tabular form.

TABLE V.—SUMMARY OF UNCOMPLICATED CASES WITH GLYCOSURIA IN THE ENDOCRIN GROUP.

Gland.	No.	With glycosuria.	
		No.	Per cent.
Pituitary	562	96	17.1
Thyroid	331	33	10.0
Gonad	204	42	20.6
Adrenal	11	5	45.5
Pluriglandular	21	4	19.0
Total	1129	180	15.9

Total per cent, excluding pituitary and thyroid, failure: 21.4.

But few comments are necessary. Outside of the thyroid with a lower and the small adrenal group with a much higher level, the incidence in the remaining series approaches a parity. The relative endocrin incidence is definitely lower than that in the selected non-endocrin groups, but if the anomalous groups of pituitary and thyroid failures be eliminated, the frequency in the glandular group is about equal to that in the other. If both the endocrin and non-endocrin groups be taken in their entirety the latter shows about half as many as the former.

As already noted, true hyperglycemia is far more suggestive of the presence of diabetes than is the occurrence of glycosuria. The number of methods for blood-sugar estimation is large, and each new addition to the group tends progressively to indicate a lower level for the norm. Since its introduction in 1920, we have used the Folin-Wu¹⁶ method, as it has proven wholly dependable and to yield reproducible results. Further, adherence to a single method of proven excellence permits of direct comparison of the results recorded over a long range of years. On the basis of this method, Joslin⁹ regards a permanent fasting blood-sugar level of 130 mg. as indicative of diabetes, if a few conditions such as nephritis without hypertension, hyperthyroidism, obstructive jaundice and cardiac cirrhosis can be ruled out. The blood-sugar values obtained with the 286 cases composing this group have been collected in the next table.

TABLE VI.—BLOOD-SUGAR LEVELS OF CASES WITH GLYCOSURIA.

Subgroup.	Nonendocrine group.		Subgroup.	Endocrine group.	
	Average mg. per 100 cc.	Over 120 mg.		Average mg. per 100 cc.	Over 120 mg.
Infections . . .	98	0	Pituitary	97	0
Psychoneuroses . .	99	0		96	3 (128 mg.)
Nervous system . .	94	0		103	0
Metabolism . . .	87	0	Thyroid	90	1 (125 mg.)
Cardiovascular . .	107	1 (140 mg.)		99	0
Blood diseases . .	94	0		99	1 (148 mg.)
Tumors . . .	95	0	Gonad	100	3 (125 mg.)
Ear diseases . . .	85	0	Adrenal	81	0
Asthma . . .	71*	0	Pluriglandular	96	0
Liver diseases . .	96	0			
Syphilis . . .	106	1 (142 mg.)			
Normal . . .	101	0			
Total . . .	97	2 (Av., 141 mg.) 2.5 per cent	Total . . .	97	8 (Av., 129 mg.) 3.9 per cent

* The case already noted.

In the main, it is clearly apparent that high blood sugars play no significant rôle in the determination of the glycosurias. But 10 exceed the conventional limit of 120 mg. and only 4 are above the Joslin critical level. These were:

1. *Case S-432.* Pituitary dysfunction probably secondary to an established brain tumor. Blood sugar, 133 mg. Galactose tolerance, -25 per cent.

2. *Case B-468.* Syphilis complicated by nephritis without hypertension. Blood sugar, 142 mg. Galactose tolerance, =0.

3. *Case S-1697.* Hypertension with renal involvement. Several suggestions of neurosyphilis but lumbar puncture refused. Blood sugar, 140 mg. Galactose tolerance, -67 per cent.

4. *Case S-1677.* Thyroid failure without myxedema. Request for repetition of blood sugar refused. Blood sugar, 148. Galactose tolerance, =0 per cent.

But 1 of the cases carries any real suggestion of a possible diabetes, and this was the only one in which the blood-sugar level was not substantiated. Later reports on this patient record complete clinical improvement under thyroid medication.

In the remaining 6 cases, whose levels were superior to 120 mg., an emotional element was present in some if not all of them.*

As individual values are absorbed in collective presentation, it should be added that the only patients showing hypoglycemic levels were in the adrenal group, where it is pathognomic, the single case of asthma under heavy suprarenin medication and the following 4 cases:

1. *Case B-127.* Pituitary dysfunction. Acromegaly undergoing functional involution. Blood sugar, 73 mg. Galactose tolerance, -67 per cent.

2. *Case B-157.* Pituitary dysfunction. Facial hemiatrophy. Blood sugar, 74 mg. Galactose tolerance, -75 per cent.

3. *Case B-112.* Traumatic lesion of central nervous system. Blood sugar, 75 mg. Galactose tolerance, -33 per cent.

4. *Case B-140.* Osteitis deformans. Mitral stenosis. Nephritis. Blood sugar, 75 mg. Galactose tolerance, -87 per cent.

For the great majority of the patients the individual levels were in reasonable approximation to the group averages. The latter are to be regarded as truly representative. For such information as is intrinsic in them, these blood-sugar values generally deny the existence of diabetes in this series of glycosurics.

* In this connection, the results obtained with a medical student some years ago are suggestive. The individual in question was a highly emotional Porto Rican whose blood chemistry was determined in the course of a routine examination. The first level of 163 mg. led to weekly examinations, under exactly the same conditions. These gave successively 148, 124 and 110 mg. His habituation to venipuncture failed to dispel his distaste for it and the series was discontinued with the attainment of a normal level.

The galactose tolerance gives information as to certain aspects of the carbohydrate metabolism. Although it is a hexose, a sugar not foreign to the usual dietary, a glycogen former and presumptively a product synthesized by the mammary glands during lactation, it seems reasonably certain that its metabolism does not parallel that of glucose in all details, although in certain general respects it differs only in degree. The present analysis is concerned with the possible origins of a glycosuria that may not be traced to pancreatic hypofunction. The assimilation limits for galactose are germane to the thesis. Not all of the patients in the series received the test which requires three days for its performance. Further, the cases presenting significant complication have been deleted. Even with these limitations, practically 70 per cent of the remaining group were examined and the results of the tests are given in the next table. To save space, only the significant groups in the non-endocrin series are included. Of the 23 cases omitted, 12 did not receive the test, 5 were normal and the remaining 6 showed an average tolerance 58 per cent below prediction.

TABLE VII.—GALACTOSE TOLERANCE OF UNCOMPLICATED CASES
IN THE MAJOR GROUPS.

Condition.	Tolerance.					
	Depressed.		Normal.	Increased.		Summation, per cent.
	No.	Per cent.		No.	Per cent.	
Psychoses	1	-67	-67
Nervous system	18	-52	3	1	+50	-40
Blood diseases	3	-50	1	-37
Tumors, malignant . . .	3	-42	1	-31
Liver diseases	12	-56	2	-48
Syphilis	6	-40	2	-30
	43	-52	9	1	+50	-41
Pituitary	{ +	5	-67	-67
	{ ±	56	-55	-55
	{ -	10	+65	+65
Thyroid	{ +	1	-75	-75
	{ ±	3	-33	4	..	-14
	{ -	6	2	+38	+ 9
Gonad	-	20	-44	1	..	-41
Adrenal	-	5	-61	-61
Pluriglandular	±	2	-67	1	..	-44

In the nonendocrin group the prevailing tendency is toward a depressed tolerance, although about one-sixth were normal. The single patient showing a tolerance above prediction was a case of the Parkinsonian syndrome following an earlier encephalitis. The urine sugar was verified as glucose. Detailed study gave no evidence of any complication which could account for the anomaly.

The larger part of the endocrin cases showed a depressed tolerance

as was to be anticipated from the functional levels of the glands involved. The majority of the normal cases were in the thyroid group, this gland exercising less influence on the galactose tolerance than the other members of the endocrin concert. The single ovarian patient with a normal tolerance was one with an established nephritic condition and lowered kidney permeability. She had had both ovaries removed some years previously, so that no question could arise as to the presenting endocrinopathy. The normal pluriglandular case presented a thyroid dysfunction superimposed upon an ovarian failure deriving from castration. The galactose tolerance of the female castrate is that of prepubertal years, namely, 20 gm., and the positive response of this patient to that dosage indicated only that the thyroid dysfunction was without significant influence, a somewhat usual finding.

The two groups of major interest in this connection are, however, those patients with failure of the pituitary and thyroid respectively. Only 2 of the latter demonstrated increased levels of tolerance and the remainder were normal. The blood-sugar levels were normal with the single exception noted above (Case S-1677) and omitting this case, the group average would be 97 mg.

Far more striking are the results with the group of bilobar pituitary failures. One of the original 11, with a tolerance of +50 per cent, presented a complicating psychosis and has been deleted. The remaining 10, however, exhibited a tolerance for galactose ranging from 33 to 100 per cent above prediction with an average of +65 per cent. In spite of this increased assimilation limit—and uniformly normal blood-sugar levels throughout—all of these patients exhibited a slight but definite glycosuria. That the different sugars imply different mechanisms is obvious, but this does not resolve the question. The whole matter will be discussed in a later communication; the fact is presented here without further comment.

There remains one other condition which should be considered in this connection. Several cases have been dropped from the preceding series on the basis of pregnancy and this condition is generally recognized as productive of an intermittent glycosuria which is due to a leakage of glucose. Lactosuria does not enter the picture normally until a few days before delivery.⁵

The figures from a small group of cases may be presented for the sake of completeness. In a series of 100 patients, studied throughout their pregnancies, 18 showed glycosuria. While these figures are slightly higher than those usually recorded, the patients in the group were examined at frequent intervals. Twelve per cent gave repeated positive tests, a figure harmonizing with other reports. None of the blood sugars exceeded 100 mg. and a few fell slightly below the conventional lower boundary of 80 mg. The average

was the low normal value of 83 mg. The sugar tolerances were in all cases below the normal for an adult woman in a state of sexual rest and agreed exactly with the data of a much larger series now in process of completion. Here, again, while it is demonstrable that diabetes may develop during pregnancy or coëxist with it, it is equally true that a certain number of pregnant women exhibit a transitory glycosuria who neither at the time nor subsequently offer any evidence of pancreatic involvement.

Discussion. The whole question is both large and highly complex. No adequate treatment of even a significant number of the ramifications may find place in a journal article. A brief discussion of a small group of implications may, however, be permitted. Ignoring completely the extremely interesting and suggestive group of non-endocrin conditions associated with glycosuria, certain of the endocrin aspects only will be considered.

In the first place it is demonstrable that the pituitary has a greater quantitative influence on sugar metabolisms than any of the other endocrin glands exclusive of the pancreas. Further, in demonstrated overactivity of the pituitary glands—for morphologically and functionally the pituitary is not a unitary structure—there is a marked depression of sugar tolerance, a slight persistent glycosuria and usually a normal blood sugar, features not uniformly characteristic of diabetes. Let us assume for the moment that one or more of the pituitary hormones exercise an antagonistic effect on insulin activity and that the results of overproduction operate through this mechanism.* It would then seem that conversely, in established hypofunction, large excess quantities of insulin should be released and the insulin effects greatly augmented. But the hypopituitary case shows none of the well-known features of hyperinsulinism. Most importantly there is no hypoglycemia. On this assumption, one is constrained to conclude either that the production of insulin is depressed, a condition in ill accord with the fact of greatly increased sugar tolerance, or that the increase in available insulin augments selectively the normal processes for the disposal of carbohydrate. But analysis of this conclusion leads to further stumbling blocks. Exclusive of the direct elimination of excess sugar by the kidney, which does not come into question in this particular case, there are but three possible mechanisms which may be brought into play. The first, storage as sugar or glycogen, has very definite limits, as the body does not possess unbounded capacity for the retention of carbohydrate. The second, combustion, is equally limited as the energetic requirements of the body are straitly defined and can be

* Even in this there is a large measure of assumption. In the Cushing and Davidoff experiments⁷ their 3 diabetic acromegalics had shown a normal response to insulin and only failed to give the expected fall in blood sugar when the insulin was mixed with pituitrin before injection.

accurately measured. Cases of pituitary failure are not infrequently encountered which can tolerate in a single test meal enough carbohydrate to provide the total energy for the entire twenty-four-hour requirement. The third, transformation of carbohydrate into fat, offers large possibilities in providing for an excess of carbohydrates, and there is some evidence that insulin will promote fat storage. Further, there is reason to believe that under certain conditions, insulin may be concerned in the transformation of sugar into fat. That it is an usual feature of insulin activity, however, may be questioned. Certainly, high respiratory quotients are not characteristic of pituitary failure. Without adducing a number of other contradictory evidences, it may be pointed out that glandular hypofunction is a chronic state and cannot be compared or contrasted with acute conditions produced by experimentation.

A similar antagonism for suprarenin toward insulin has been demonstrated by several and in this report come yet other seeming obstacles. Addison's disease, with destruction of the glands demonstrated at autopsy, may reasonably be regarded as involving an hypofunction of the adrenals, though possibly including other factors in the complete picture. Underfunction should produce low blood sugar by a lowering of the inhibition of insulin activity and as a matter of fact, hypoglycemia is pathognomic of the condition. But, unfortunately, it should also raise the sugar tolerance—and controlled experience demonstrates that the converse is the case.

As stated at the beginning of this discussion, the problem is a vast one and even a very partial discussion would far exceed any permissible limits.

It seems warrantable to conclude, however, from the facts set forth in this paper, that the appearance of sugar in the urine is but a single end result of a large number of causes. Further, many of these can with difficulty, if at all, be interpreted as operating through the mechanism that produces the same end result in pancreatic diabetes. That insulin after it has left the pancreas or any of the body storage places may be involved in some of the other glycosurias may be freely conceded, but that it is the decisive factor in all must be equally definitely denied.

Summary. 1. The etiologic background has been studied of a number of cases showing glycosuria but without demonstrable evidence of a diabetic condition.

2. Certain nonendocrin states, including psychoses, lesions of the central nervous system, primary anemia, lymphatic leukemia, malignant neoplasm, various types of hepatic dysfunction and syphilis, have shown a distinctive frequency of incidence of glycosuria. Further, certain of these conditions have appeared as complicating factors, in a group of patients with glycosuria whose primary complaint was not included in the list given above.

3. Analysis of a similar series of disturbed endocrin functional states shows a similar incidence of glycosuria, even after those have been deleted which present the significant nonendocrin disorders as secondary complications.

4. With but minor exception, all of the individuals show normal blood-sugar levels and the several group averages are entirely within conventional limits.

5. The majority of the patients in the series show a depressed tolerance for galactose which is characteristic of the several conditions involved.

6. Exception to the foregoing is noted in the case of thyroid failure, and far more strikingly in hypofunction of the pituitary, where increased galactose tolerance is occasionally associated with glycosuria.

7. The same condition of glycosuria with normal blood sugar is noted in the physiologic state of pregnancy.

Conclusion. 1. It is concluded, that the phenomenon of glycosuria is no more than one common end result of a wide variety of causes, many of which cannot be demonstrated to produce the effect through influence on or by the function of the pancreas.

2. From this it is deduced that there are a number of factors concerned with the regulation of carbohydrate metabolism, of which the intrinsic function level of the islands of Langerhans, although most important, is but one.

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EMOTIONAL HYPERTENSION.

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It has long been known that emotional stimuli cause variations in the arterial tension. These variations are encountered both with conscious and subconscious emotional changes. During sleep the systolic arterial tension falls, usually as much as 20 mm.^{1,2,3,4,5} When sleep is restless and disturbed by dreams extraordinary elevations in arterial tension have been recorded.⁶ Such marked and rapid fluctuations as may occur during restless sleep constitute a very real menace to individuals with hypertension in whom the sudden rise may be responsible for cerebral, pulmonary or gastrointestinal hemorrhages.⁶ The emotional state when awake plays an important rôle in the causation of temporary fluctuations in the blood pressure. The observation that the arterial tension is higher on the first visit of a patient than at later periods is common knowledge. Frequently the blood pressure is found considerably higher by an examiner for a life insurance company than the applicant's own physician ever finds it. This is largely because of the emotional tension attendant to such examinations.

The rise in arterial tension associated with emotional excitement is exaggerated in individuals with vascular disease and arterial hypertension. The most frequent factors in producing temporary arterial hypertension in young individuals are nervousness and excitement.⁷ Notable increases in blood pressure occur in psychoneurotic individuals under mental strain or with anxiety neuroses.^{8,9} The diastolic tension in epilepsy is extremely labile.¹⁰ Moderate variations are noted in normal individuals if frequent repeated observations are made.¹¹ No positive correlation is found between the height of the blood pressure and its variability.¹²

The variations in arterial tension discussed above are notably asymptomatic. Change in arterial tonus with resultant fluctuation in the peripheral resistance to the circulation is dependent upon vasomotor stimuli. Emotional vasoconstriction or dilatation may be quite localized, as shown by the facial blanching or blushing upon fear or embarrassment. The ordinary blush, however, is not associated with any gross change in the general systemic blood pressure. It is unnecessary here to consider the neurologic control of the vascular tone and its mechanism; it suffices to state that vasomotor stimuli may arise from emotional activity and cause distinct elevation of the systemic arterial tension.

Exaggeration of a physiologic phenomenon may form a pathologic

phenomenon. Minor fluctuations of 15 to 20 mm. of pressure occurring under conditions of psychic strain are normally physiologic.^{11,12} Extreme instability of the arterial tone, resulting in such exaggerated responses as fluctuations of 50 mm. or more in the arterial tension can no longer be considered physiologic. It is with such instances of vasomotor instability that the present report deals. The subjective manifestations of this interesting neurocirculatory phenomena are so variable that careful observation is often necessary to elicit the real foundation for the complaints.

Analyses of Cases. During the last year it has been our privilege to see and study 8 cases of extreme vascular instability associated with emotional hypertension. Of these cases, 7 were women. The average age was thirty-seven years, the maximum age being fifty-three and the minimum age twenty-five years. All the patients had normal arterial tension when at rest. The average blood pressure for the group was 126/80 at rest and 173/109 after psychic excitement. In all instances this psychic hypertonia was associated with definite subjective distress. In 6 out of the 8 cases the subjective distress constituted the reason for seeking medical advice. Such an average rise in arterial tension of 47/29 on mental excitement surely must be considered pathologic. The maximum rise in any patient under the stress of emotional strain was 60/32.

As many of these patients complained of emotional instability, a possible connection of the vasomotor instability with hyperthyroidism was considered likely.¹³ Such a connection does not exist, however, as in 5 particularly suspicious instances in the series, determination of the basal metabolic rate revealed rates well within normal limits.

The subjective complaints are enumerated below:

SUBJECTIVE COMPLAINTS IN 8 CASES OF EMOTIONAL HYPERTENSION.

Emotional instability	5
Sexual abnormalities	6
Urticarial blotching on emotional strain	2
Flushing and sense of heat on emotional strain	2
Precordial constriction on emotional strain	2
Precordial pain on emotional strain	1
Choking sensations in throat on emotional strain	1
Epigastric distress on emotional strain	1
Cephalalgia on emotional strain	1
Apokamnosis on emotional strain	1

The relationship of sexual abnormalities is particularly interesting. All the 6 instances of abnormality occurred in women. In 3 a distressing borderline nymphomania occurred; 2 complained of frigidity, 2 had been sterile for three or four years, although they wanted children; 1 had had the pelvic organs removed with an artificial menopause. A relationship of ovarian activity and change in the arterial tension is frequently observed also in instances of

excessive masturbation.¹⁴ The vascular instability associated with the menopause is well known.^{15,16} It is probable that some physiologic connection exists between gonadal activity and the stability of vasomotor control.¹⁷ Any relationship to the adrenal secretion of epinephrin is doubtful, as it has been shown that intense and prolonged emotional disturbance causes no effect upon the store of epinephrin, although numerous drugs diminish it greatly.¹⁸

The symptomatology is best illustrated by specific case reports. Four of these suffice to reveal the type of clinical pictures met with and to emphasize the variability of the presenting symptoms. One factor is common to all—the presenting symptoms are brought on by emotional strain and not by exertion.

Case Reports. CASE I.—(P.A.H.1.) A young married woman, aged twenty-six years, with a ten months' old baby, complained of a continuous sense of nervous tension with much emotional instability. Prior to her marriage she had been conscious of sexual repression and now suffered from a mild nymphomania. Had marked and uncontrollable phobias for crowds, elevators, trains and automobiles with a sense of panic. On such panic, on embarrassment or with unsatisfied sexual desire, she noted what she called "heart attacks." These never occurred with exertion, even on climbing three flights of stairs carrying the baby, although during her college life she was forbidden gymnasium work because of presumed cardiac disease. The attacks were said to consist of a sense of compression in the chest with a slow, pounding palpitation and some slight air hunger. There was no aura and the precordial distress lasted ten to fifteen minutes.

During 1918 she had suffered from a severe influenza. Her pregnancy in 1927 was uneventful except for severe hemorrhage on delivery because of a placenta previa. Habits were excellent. Examination revealed no evidence of cardiac disease. The pulse was 88, regular and no cardiac enlargement, murmurs or thrills could be elicited. The arterial tension was 130/85. On embarrassment the patient immediately complained of having an "attack;" the arterial tension was then 190/120. The urine was normal; the hemoglobin, 80 per cent (Dare). The basal metabolic rate was +5. Her response to exertion was good.

Reassurance to the effect that there was no cardiac disease and explanation of her distress assisted in calming some of the emotional instability and panic. On a second occasion, a week after the first observation, the blood pressure rose from 120/70 to 180/108 on excitement. Patient was given bismuth subnitrate (10 gr.), three times daily. In two months the distressing symptoms of panic and precordial distress had completely subsided and the instability of the arterial tension was much reduced—rising from 120/70 to 135/85 on emotional strain.

CASE II.—(P.A.H. 2.) A married woman, aged fifty-three years, complained of flushing about the head, vertigo, palpitation with tachycardia and cardiac consciousness occurring on emotional strain. Menopause had been induced by radium ten years previously. In 1918 the patient suffered severely from influenza with a considerable degree of residual myocarditis as a sequel. Chronic constipation and an irritable colon had been present for years. Habits were excellent.

Physical examination revealed nothing of moment. The heart was normal to percussion and auscultation, and exertion caused no undue distress. The arterial tension was 130/90 but with the stimulus of fright rose

to 170/110, with typical vertigo, precordial distress and tachycardia, as described above. The basal metabolic rate was -19 . Therapy with Lugol's solution and bismuth subnitrate, 10 gr., three times a day, gradually gave complete relief. To date there has been no recurrence.

CASE III.—(P.A.H. 7.) A young, unmarried woman, aged twenty-eight years, complained of great emotional instability and a sense of continuous tension. On emotional reaction she was much distressed by the appearance of large urticarial blotches about the throat and chest, which persisted for ten to fifteen minutes. Occasionally emotional strain produced acute sense of heat about the head. Past history essentially uneventful. Familial environment had been that of great nervous tension. Had been most unhappy as a girl, resorting to moderate masturbation. Since maturity has been distressed by sexual impotence and leucorrhea.

Physical examination revealed nothing of moment, other than the instability of the vascular tension. At rest this was 120/70 but rose to 158/108 with merely slight psychic stimulus. Anemia was present, the hemoglobin being but 62 per cent (Dare).

Therapy with bismuth subnitrate, as in the other patients, led to a great reduction in emotional instability and the associated vasomotor phenomena which distressed her. The patient became much calmer and found herself more capable of concentration in her work as an actress. The instability in vascular tone was simultaneously reduced.

CASE IV.—(P.A.H. 5.) A young divorcee, aged twenty-nine years, active in business, was first seen in June, 1929, complaining of severe attacks of "choking," which consisted of a sense of severe constriction in the throat, air hunger and precordial oppression. These attacks were not associated with exertion, but with any excitement and particularly erotic emotions. For many years the patient had noted emotional instability and some undue dyspnea upon exertion.

The past history was unilluminating except for the admission of similar attacks previously at the time of mental strain associated with her divorce. Had always been sexually conscious and had encountered much difficulty in repressing the tendency to nymphomania. One sister is a pronounced nymphomaniac. Examination revealed a slightly enlarged, soft, symmetrical thyroid but no tremor, exophthalmos or tachycardia. The pulse was S_4 ; the basal metabolic rate was $+9$. Examination of the heart revealed no abnormalities. The arterial tension was 120/70, but rose suddenly to 180/102 with acute choking distress on discussion of erotic problems. Later a spontaneous attack of distress occurred, at which time the arterial tension was 170/102. The charting of respirations during the basal metabolism test showed three regular cycles of hyperpnea which were not related to physical activity.

Therapy with bismuth subnitrate led to moderate improvement, but complete relief from all the distressing symptoms occurred when erotic stimulation was avoided.

Comment. The pathogenesis of this emotional vasomotor instability is not clear. In some way the normal equilibratory mechanism of the circulation is disturbed and an exaggerated, uncompensated response of generalized vasoconstriction occurs on psychic stimulation. The chief source of change in the peripheral resistance to the circulation, or the diastolic pressure, lies in arteriolar constriction. This constriction is dependent upon a constant flow of

impulses along the sympathetic nerve fibers to the smooth muscle in the arterial walls. Vasomotor nerves contain both constrictor and dilator fibers.¹⁹ Hypertension may be defined as an "irritable vasomotor condition."²⁰ In so-called "essential" hypertension the arteriolar hypertension becomes relatively continuous. Not so here, for under conditions of psychic rest these patients all displayed normal blood pressures.

In addition to the extreme lability of the vasomotor apparatus as observed in these patients, the factor of habit must be given consideration. It has been pointed out that a vessel by constant use of its power of contraction may acquire the habit of so responding to the same degree when the stimulus is lessened or when another form of stimulus is received.²¹ Fatigue of the arteriolar musculature increases its irritability¹⁷ and so exerts an influence in the perpetuation of this instability.

Heredity may play some rôle in the production of such arterial instability,²² as the majority of these patients are emotionally similar. They are tense, absorbed, unable to relax and often depressed.²³ Physical characteristics are not noteworthy. Endocrinologic faults of hereditary origin are not unlikely etiologic factors. No clinical evidence of adrenal dysfunction was encountered in these patients. That hyperthyroidism is not a factor is indicated by the normality of the basal metabolic rates of these patients. There does appear to be a rather close relationship to gonadal activity, however. It has been observed that the average blood pressure of women with abnormal menstrual function is higher than in the normal.²⁴ It is probable that at least some part of the ovarian hormone acts to reduce arterial hypertonia. The symptomatology presented by this series of patients with acute emotional hypertension rather closely resembles that of the climacteric.¹⁵ Only 1 patient of the series, however, had reached the menopause.

As yet, it is impossible to say whether the primary fault lies in an inherent emotional or psychic instability with constant turmoil or whether this emotional instability results from the circulatory disturbance. An identical question is presented by the restless mental flutter and inability to concentrate in long-standing arterial hypertension.¹⁷ In therapeutic attack upon both problems the results are very similar whether emotional sedatives, such as sodium bromid, or vascular sedatives, as bismuth subnitrate, are employed.^{26,27} Reassurance and intimate coöperation between patient and physician can do much to calm the troubled waters of emotional storms.²⁵ Control of the emotional tension by physical rest is neither practical nor effective in instances such as these. Small doses of sodium bromid, 10 gr., three times per day, as used in the therapy of persistent hypertension,²⁸ are of some value. Attention to the gonadal factor with organotherapy should theoretically be a most important mode of therapeutic attack, but so little is known and so much

surmised regarding the hormones of the sex glands that as yet there is no rational therapeutic agent available.

In our own experience, better and more permanent therapeutic results are obtained in hypertension of spastic origin with bismuth subnitrate as a vascular sedative.^{26,27} The pharmacodynamic action of bismuth subnitrate is that of minute continuous doses of nitrite ions. Instead of the violent, fleeting, quickly transient, vasodilatation obtained with the soluble amyl nitrite or nitroglycerol, a prolonged and persistent arterial relaxation occurs. Bismuth subnitrate is but very slowly soluble, so that a continuous liberation of NO_3 occurs in the bowel; in the presence of *Bacillus coli* the NO_3 is reduced to NO_2 .²⁶ Through such persistent, mild vascular relaxation by the nitrite ions vascular rest reduces the arteriolar irritability. As in angina pectoris,²⁷ the value of bismuth subnitrate in these instances of vasomotor instability is in part prophylactic, in acting as a snubber to the spastic, erratically contracting arterioles. It offers the most physiologic type of therapy here.²⁹

The symptoms presented by these patients are all directly attributable to circulatory disturbances. The one common characteristic is the association of these disturbances with emotional reactions, particularly with fear, anger, dread or erotic storms. In this respect the cardiac symptoms, such as precordial distress, thoracic constriction, palpitation, dyspnea or choking may be sharply differentiated from those arising from true cardiac disease. With reduction of the cardiac reserve, distress arises upon exertion, not upon psychic effort. The cutaneous symptoms of urticarial flushing and asymmetric perspiration are the result of local vasomotor disturbance. It is possible that the severe choking sensation complained of by one patient (Case IV) was in part due to angioneurotic edema of the upper respiratory passages. Cyanosis of the hands has been reported as being a valuable presumptive sign of hypertension.³⁰ Vertigo and cephalalgia during these vascular crises are undoubtedly due to impairment of the cerebral circulation.

The prognosis in such emotional hyperpiesia is as yet unsettled. This characteristic picture probably represents the earliest stage in the development of so-called "essential" hypertension. A permanent hypertension may later develop on a basis of such unusual nervous and vasomotor irritability.³¹ The majority of patients with hypertension reveal the so-called nervous temperament.³² The later anatomic changes in the arterial structures occurring in persistent hypertension are most probably the result of continued hypertonia.^{33,34,35,36} Early correction of emotional hypertension apparently prevents any permanent vascular damage, but recurrences must be watched for. It is suggested that this form of disturbed vascular tension should be considered as "potential arterial hypertension." Such extreme vasomotor instability represents a precursor to vascular disease with arterial hypertension. Per-

sistence of hypertonia leads inevitably to fatigue of the arteriolar musculature and, with fatigue, hyperirritability occurs and, therefore more spasticity and additional fatigue. Thus a vicious circle is set in motion, which probably is a most significant "perpetuating factor" in the pathogenesis of arterial hypertension.¹⁷

Summary. Exaggeration of the vasomotor response to emotional stimulation causes an acute arterial hypertension in certain patients, with associated subjective symptoms. The rise in arterial tension is so marked as to constitute a definite menace to physical health. The symptoms are quite variable, being referable to the cardiac apparatus, the head, cutaneous sensations and the respiratory functions. The symptoms are all physiologically dependent upon vasomotor phenomena. Emotional instability is characteristic of this group. Sexual disturbances are likewise frequent and notable.

Such emotional hypertension may form the basis of later permanent arterial hypertonia. It, therefore, may well be considered as a "potential hypertension." This clinical syndrome must be sought for by blood-pressure observations, in all instances where patients complain of physical distress attendant upon psychic strain. The emotional instability so characteristic of these vasomotor phenomena may be the result of the circulatory instability, or *vice versa*. Thus far, the most satisfactory method of therapy has been the administration of bismuth subnitrate in 10-gr. doses, thrice daily, as a vascular sedative and depressant, combined with reassurance. It is important that these patients be thoroughly convinced that they are not suffering from heart disease, as many of them believe.

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THE ARTHRITIC COMPLICATIONS OF GONORRHEA IN THE ADULT MALE.

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THERE is division of opinion concerning the rôle of the urethral infection in the etiology of gonorrheal arthritis. There are two views: (1) That the arthritis is a manifestation of a gonococcal septicemia; (2) that the arthritis is a distant result of focal infection in prostate or seminal vesicles.

According to the first view, gonorrheal arthritis is comparable to arthritis developing during the course of pyogenic infections, pneumonia and other infectious diseases. The factors concerned are the virulence of the organisms and the resistance of the patients.

According to the second view, gonorrheal arthritis follows extension of the urethral infection to the prostate and seminal vesicles.

Methods of treatment are numerous. As they are all based on either of the above theories, they may be divided into nonfocal and focal measures.

Some examples of nonfocal measures are: (1) Vaccines and foreign proteins to promote antibody formation; (2) immobilization of the affected joints—on the grounds that the gonococcal infection is self-limited; (3) the use of heat, diathermy or irrigation through

surgical incision of the joint capsule to destroy the organisms around the joints.

Focal measures are represented by seminal vesiculotomy; seminal vesiculectomy; medication of the vesicles by various means; massage of the prostate and vesicles.

The current literature of the disease deals mainly with the value of particular methods of treatment. Good results have been obtained in some cases with every method. Usually the immediate result is considered the measure of effectiveness. There is a tendency to ignore clinical types; to credit cures to the remedy and bad results to the obstinacy of the disease.

It is well to remember that all the clinical characteristics of gonorrheal arthritis were described before the discovery of the gonococcus. They were thoroughly studied by observers who believed in the specific nature of the affection, as opposed to those who doubted the likelihood of gonorrhea being the cause of a distinct form of "rheumatism." After the discovery of the gonococcus these clinical features were considered gonococcal in the sense that gonococci cause a form of arthritis that differs, in some respects, from that caused by other bacteria.

The rôle of the urethral infection in the etiology of gonorrheal arthritis can be determined only by study of these clinical features with relation to the focal theory, that is, by clinical investigation of the urologic lesions associated with the various types of arthritis.

This paper consists of a study of 28 cases from this standpoint.

Case Reports. CASES IN WHICH ARTHRITIS DEVELOPED DURING ACUTE GONORRHEA. CASE I.—Nine days after gonorrhea, patient developed chill followed by temperature of 103° F.; left hand swollen and painful. Patient examined following day; circumscribed area over extensor tendons of left hand swollen, hot, red, painful and tender; seminal vesicles not palpable; prostate slightly soft and felt hot. Patient advised to stay in bed; no local treatment. Next day the temperature was normal and arthritis subsiding; four days later the hand was normal. The urethritis responded to routine treatment.

One year later, no recurrence of arthritis; prostate normal, vesicles not palpable; secretion normal.

Comment. The acute onset of the arthritis and the heat over the prostate suggests that absorption in this case was from the prostatic urethra. Rest in bed was sufficient to cause subsidence. No other similar case has been encountered.

CASE II.—Seventeen days after gonorrhea, lumbar back painful on motion and at rest unless supported; right knee painful on motion but not swollen or discolored. Roentgen ray; no pathologic bone changes. Prostate slightly boggy; seminal vesicles palpable but not hot. Treatment consisted of urinary sedatives and hot sitz bath twice daily. Arthritis subsided in three days; urethritis responded to treatment. One year later, no recurrence of arthritis; prostate normal; vesicles not palpable; secretion normal.

CASE III.—Seventeen days after gonorrhea, dorsal aspect left wrist and metacarpophalangeal joint of left thumb painful and slightly swollen; no

heat or discoloration. Prostate slightly soft; both vesicles palpable but not hot; paraphymosis. Treatment, paraphymosis reduced; hot sitz bath twice daily. Arthritis subsided in four days. Six months later, no recurrence of arthritis; prostate slightly soft; vesicles not palpable; secretion, living spermatozoa, 40 to 50 pus cells to high-power field.

CASE IV.—Twenty days after gonorrhea, dorsal aspect of left wrist painful and slightly swollen; left knee painful on weight bearing; slight swelling of both sides of patella. Prostate slightly soft; left vesicle palpable; right vesicle not palpable. Treatment, hot sitz bath twice daily. Arthritis subsided in four days. Four months later patient contracted another gonorrhea, seminal vesicles not palpable, no arthritis. One year later, no recurrence of arthritis, prostate slightly soft, vesicles not palpable, secretion, living spermatozoa, 15 to 20 pus cells to high-power field.

Comment on Cases II, III and IV. In these cases the affected joints were painful; but swelling, when present, was slight, and there was no heat or redness. Both seminal vesicles were palpable in Cases II and III and the left vesicle was palpable in Case IV; heat was not noted over the vesicles in any of these cases. The arthritis subsided in all cases in a few days.

The acute joint inflammation of gonorrheal arthritis is often preceded by pain and slight swelling of the joints. Cases such as these, in which the joint involvement subsides instead of advancing to the stage of acute inflammation, are occasionally encountered. They may form the basis for claims for effectiveness of various remedies in checking the advance of gonorrheal arthritis.

The explanation offered here is that the arthritis subsided because the process in the vesicles subsided and absorption stopped. Had the involvement of the vesicles continued to the stage of acute seminal vesiculitis the joints would have become acutely inflamed.

CASE V.—Duration, three days. Acute inflammation of extensor tendons of right hand and wrists; right knee painful on motion. Seminal vesicles not palpable but increased heat noted over right vesicle area.

CASE VI.—Duration, seven days. Acute inflammation of extensor tendons of left hand and wrist. Left seminal vesicle palpable and hot; right vesicle palpable.

CASE VII.—Duration, eight days. Acute inflammation of tendons over instep of left foot; both shoulders, dorsal and lumbar back painful. Both vesicles palpable and hot.

CASE VIII.—Duration, eight days. Acute inflammation of tendons around external malleolus of both feet. Both vesicles palpable and hot. Stricture of small caliber in anterior urethra.

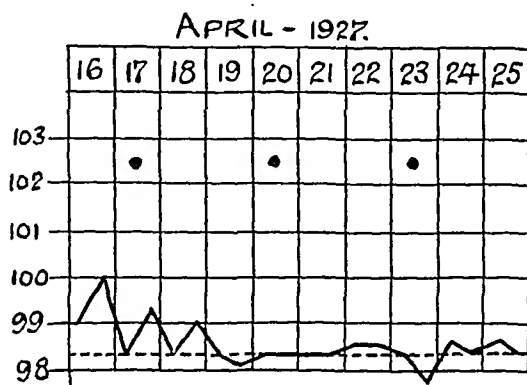
CASE IX.—Duration, sixteen days. Acute inflammation of extensor tendons of left hand and wrist; muscles of forearm wasted. Both vesicles palpable and hot.

CASE X.—Duration, eighteen days. Acute inflammation of extensor tendons of right hand and wrist and involving flexor tendons of wrist; acute

inflammation of periarticular tissues of left ankle. Both vesicles palpable and hot.

CASE XI.—Duration, twenty-three days. Acute inflammation of extensor tendons of left hand and wrist and periarticular tissues of right ankle. Both vesicles palpable and hot.

CASE XII.—Duration, forty days. Acute inflammation of periarticular tissues of right knee, both ankles and metacarpophalangeal joint of right thumb; lumbar back and right temporomandibular joint painful on motion. Both vesicles palpable and hot.



• = INJECTION OF VESICLES

CHART I.—Temperature chart of Case XII.

Comment on Cases V, VI, VII, VIII, IX, X, XI and XII. These are typical examples of acute gonorrheal arthritis in the stage of acute joint inflammation. Gonococci were present in the urethral discharge in every case. The arthritis developed in from five to thirty-three days after gonorrhea. Roentgen-ray studies showed decalcification of the bones of the acutely inflamed joints at some time during the course of the disease.

One or more of the affected joints in each case were swollen, hot, reddened and tender. Acute inflammation of the seminal vesicles was denoted in each case by the presence of heat over one or both of these organs.

The arthritis was unilateral in Cases V, VI and IX and in Cases V and VI the acute vesiculitis was unilateral and on the same side as the arthritis. The arthritis was bilateral in Cases VII, VIII, X, XI and XII and the acute vesiculitis was bilateral in these cases.

These findings indicate that the acute arthritis is dependent upon the acute vesiculitis and that the duration of the acute joint inflammation depends upon the duration of the acute vesiculitis.

These patients were treated by the injection of Pregl's solution into the seminal vesicles through the rectal mucosa as first described by Stellwagen in 1925.¹ This procedure checked the absorption from the vesicles and in each case the acute inflammation of the

joints subsided; that is, pain became less severe, swelling decreased and heat and redness disappeared.² The injections were also followed by decline in the fever. It may be inferred from this action of the injections that the fever in such cases depends upon the acute vesiculitis. The temperature chart of Case XII is presented as being typical of the group.

Further treatment consisted of massage of the prostate and vesicles in order to rid these organs of infection. This was started as soon as it was thought that the vesicular inflammation had subsided sufficiently to permit of massage without danger of causing exacerbation of the vesiculitis with recurrence of the arthritis. Further improvement in the arthritis consisted of gradual decrease in the periarticular swelling, gradual increase in mobility of the joints and gradual decline with eventual disappearance of pain on motion.

In Cases VI and X the patients failed to report after subsidence of the acute arthritis.

All the other patients were under observation, either continuously or at intervals, until complete subsidence of the arthritis and were examined at subsequent intervals. Relevant data on the subsequent condition of the joints and prostate and vesicles follows:

SUBSEQUENT CONDITION OF CASES V TO XII. CASE V.—One year after discharge: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; secretion after massage; living spermatozoa; no excess of pus.

CASE VII.—Six months after onset: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells to high-power field.

CASE VIII.—One year after onset: No symptoms of arthritis; Roentgen ray, no pathologic bone changes; secretion after massage, normal; stricture dilated to 30° F.

CASE IX.—Discharged from hospital in twenty days: Acute inflammation subsided, but there was marked periarticular thickening of left wrist. One year later, without subsequent treatment, slight periarticular thickening, grip normal and muscles of forearm normal; Roentgen ray, decalcification of bones and narrowing of joint space; prostate boggy; vesicles palpable; secretion, 100's pus cells; culture, pneumococci and Gram-negative bacilli belonging to the Friedländer group. Two years later, without intervening treatment, left wrist normal clinically; Roentgen ray: narrowing of the joint space and no pathologic bone changes except for fracture of lower end of radius which is united in good position. (Patient had sustained a Colles fracture.) Prostate soft; vesicles palpable; secretion, 100's pus cells.

CASE XI.—One year after discharge; no symptoms of arthritis; x-ray, no pathologic bone changes; prostate normal, vesicles not palpable; secretion, normal.

CASE XII.—Two years after discharge; no symptoms of arthritis; x-ray, no pathologic bone changes; prostate normal vesicles not palpable; secretion normal.

Comment. Recovery from the arthritis was complete in each of these cases. However, recovery from the arthritis should not be accepted as the sole standard of cure. Cure cannot be considered complete unless infection is eradicated from the prostate and seminal vesicles. This is illustrated in Cases V, VIII, XI and XII.

CASES IN WHICH THERE WAS PERSISTENCE OF JOINT DISABILITY AFTER GONORRHEAL ARTHRITIS. CASE XIII.—Four months after gonorrheal arthritis: Left knee still slightly swollen; restriction to full extension and flexion; muscles above and below knee wasted; patient unable to bear full weight on left knee and uses crutches; slight swelling metacarpophalangeal joint of right thumb; right shoulder painful on motion. Roentgen ray: irregular areas of marked decalcification of bones of left knee; small quantity of fluid in joint. (Figs. 1 and 2.) Prostate slightly soft; both vesicles palpable and tender; secretion, nonmotile spermatozoa, 70 to 80 pus cells to high-power field; no gonococci; culture, no growth at end of seventy-two hours. Treatment, vesicles injected with Pregl's solution; later, massage of prostate and vesicles; left knee baked in Orthopedic Department; patient resumed work in six months. Two years later, no recurrence of arthritis; Roentgen ray, no pathologic bone changes (Fig. 3); prostate normal; vesicles not palpable; secretion, normal.

CASE XIV.—Both heels painful since gonorrheal arthritis seven years ago. Operation for removal of spurs from both heels three years ago with no relief from pain. Roentgen ray: advanced hypertrophic osteoarthritis of bones of both feet. Prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells; culture, *Staphylococcus albus*.

CASE XV.—Bony ankylosis of right wrist nine months after gonorrheal arthritis which was treated by cast. Prostate slightly soft; vesicles barely palpable; secretion, nonmotile spermatozoa, 80 to 100 pus cells to high-power field.

CASE XVI.—Partial ankylosis of right wrist and metacarpophalangeal joints of right middle, ring and little fingers, three months after gonorrheal arthritis. Roentgen ray, general decalcification of the bones of the right hand and wrist; the articular cartilage between the carpal bones has been absorbed. Prostate normal; vesicles not palpable; secretion, normal.

Comment on Cases XIII, XIV, XV and XVI. A tendency to chronicity is widely believed to be a necessary clinical feature of gonorrheal arthritis.

Joint disability after the subsidence of the acute stage of the disease is due to the persistence of subacute inflammation of the joints, to ankylosis or to the gradual development of osteoarthritis. It is questionable whether these complications are always due to chronicity in spite of treatment rather than to improper treatment. Proper treatment should aim at the prevention of these complications.

The means of prevention should be sought in study of the relationship between the urologic lesions and the joint lesions. The significant fact of this relation is the association of the subsidence

of the acute joint inflammation with the subsidence of the acute vesiculitis.

In the stage of subacute joint inflammation the vesicles are palpable but not hot. Absorption from such vesicles may cause the continuance of subacute inflammation of the joints which may be followed by osteoarthritic bone changes. Osteoarthritis may also occur insidiously, that is, without inflammation of the parts.

Case XIII is an example of the continuance of subacute joint inflammation due to the continuance of absorption from the vesicles. Focal treatment resulted in complete recovery.

Measures directed solely to the joint inflammation are recommended by some writers in such cases. The good results attributed to this form of treatment are due rather to spontaneous subsidence of absorption from the vesicles. In cases in which absorption from the vesicles continues nonfocal measures, such as drainage of the joint, are apt to be followed by the tragedy of bony ankylosis.

Case XIV is an example of the development of osteoarthritis after apparent recovery from gonorrheal arthritis. This is an example of the futility of nonfocal measures (which in this case was the removal of spurs) in the presence of absorption from the vesicles. This patient had three attacks of iritis and, on medical advice, had his tonsils and several teeth removed, but was never given an examination of the prostate and vesicles.

Case XV is an example of the spontaneous subsidence of gonorrheal arthritis. Two joints were originally affected; treatment of one joint by means of a cast resulted in bony ankylosis. The patient also had persistence of infection in the vesicles. In view of the possibility of osteoarthritis from this source, the vesiculitis must be considered almost as grave a complication as the ankylosis. While it is true that not all infected vesicles are focal areas, still it is impossible to be sure that absorption will never take place.

Case XVI illustrates the tendency that the disease, at times, exhibits to spontaneous recovery. There was spontaneous subsidence of the focus and unaided eradication of infection from the prostate and vesicles.

CASES IN WHICH RECURRENCE OCCURRED AFTER APPARENT CURE OF GONORRHEAL ARTHRITIS. CASE XVII.—In 1918 gonorrheal arthritis of right knee for nine months. In 1921 both ankles painful and swollen and both heels painful; unable to work since 1922. In 1924 osteophytes removed from both heels with no relief from pain.

Patient first seen, March, 1925; both heels, right knee and left shoulder painful; walks with difficulty. Prostate boggy; both vesicles palpable. Vesicles injected; later prostate and vesicles massaged. Patient returned to work in two months and did not report for further treatment.

In October, 1928, recurrence of arthritis for four weeks; metacarpophalangeal joint of left great toe painful and slightly swollen; both heels painful, interphalangeal joint of left thumb painful and slightly swollen. Roentgen ray: no pathologic changes of bones of left thumb, there is decalcification of the bones of both feet, flattening of the left os calcis, general osteo-

arthritis of the bones of the left foot, particularly the tarsal bones, osteoperiostitis of the right os calcis. Prostate slightly soft, vesicles palpable, secretion, 90 to 150 pus cells to high-power field. Arthritis again responded to focal treatment.

CASE XVIII.—In 1921 gonorrheal arthritis of both feet, knees and hips, afflicted for about eighteen months. In September, 1926, both knees and ankles swollen and slightly painful. Roentgen ray: there is a small spur on the posterior-inferior angle of the right patella and a smaller spur in the same position on the left patella, there is general decalcification of the bones of both feet with a small spur on the under surface of both os calci. (Fig. 4.) Prostate, areas of induration in both lobes, both vesicles palpable, secretion, 50 to 100 pus cells to high-power field, culture, no growth at end of seventy-two hours. Arthritis responded to focal measures.

Two years later patient had received massage of prostate and vesicles every three months, no recurrence of arthritis. Roentgen ray: there is no increase in the size of the spurs on the patella or os calci and the bones of both feet show return of normal bone salt content. (Fig. 5.)

CASE XIX.—In 1918 gonorrheal arthritis of both knees and ankles. In May, 1927, pain and slight swelling of right knee, anterior arch of right foot and left ankle. Roentgen ray: large osteophyte on the under surface of both os calci. (Fig. 6.) Prostate slightly soft, both vesicles palpable. Arthritis responded to focal treatment.

Two years later, no symptoms of arthritis. Roentgen ray: no increase in the size of the spurs. (Fig. 7.) Prostate normal, vesicles not palpable, secretion, normal.

CASE XX.—In 1919 gonorrheal arthritis of both knees and ankles; joints swollen for four months and painful for another year. In January, 1927, right ankle, both knees, left great toe and right thumb painful and swollen; arthritis gradually subsided in all joints except right thumb, although right ankle was sore and painful at times. Patient first seen, March, 1928, with right thumb painful and swollen at interphalangeal and metacarpophalangeal joints; both ankles normal clinically, but right ankle becomes sore and painful after day's work. Roentgen ray: right thumb, no pathologic bone changes; right ankle, large osteophytic spur on the anterior and external aspect of the lower end of the right tibia; decalcification of the lower end of the fibula, the external aspect of the lower end of the tibia and the external aspect of the astragalus; there is irregularity of the external aspect of the astragalus and a circular area of bone infection in the superior, external aspect of the astragalus. (Fig. 8.) Prostate normal; vesicles barely palpable; secretion, normal prostatic fluid, mucous with entangled nonmotile spermatozoa and few pus cells; culture, no growth at end of forty-eight hours. Treatment, massage once monthly.

Ten months later, right thumb normal clinically and not painful for past eight months; right ankle still sore at times. Roentgen ray: there is definite, although moderate, improvement in the osteoarthritic changes in the right ankle. There is a general increase in the bony density of the structures around the external aspect of the ankle. The external aspect of the astragalus is more regular. The chronic bone abscess cavity is slightly smaller and bone condensation has occurred around its circumference. (Fig. 9.)

CASE XXI.—In 1906, gonorrheal arthritis of ankles, knees, shoulders, wrists and elbows; in bed eighteen months and crippled four years. In 1915, recurrence in shoulders, elbows, wrists and fingers; well in about

three months. In 1927, recurrence in both shoulders, knees, wrists and left thumb; in bed two months. In May, 1928, left shoulder still painful on raising arm high; metacarpophalangeal joint of left thumb slightly swollen and painful. Roentgen ray: bursitis of left shoulder; no other pathologic bone changes. Prostate normal; vesicles not palpable; secretion, nonmotile spermatozoa, 30 to 50 pus cells to high-power field.

Comments on Cases XVII, XVIII, XIX, XX and XXI. Liability to recurrence is another clinical feature widely believed to be characteristic of gonorrheal arthritis.

The facts of the relationship between the joint lesions and the urologic lesions, as shown in the study of these cases, indicate rather that recurrence should be considered a preventable complication.

Infection was present in the seminal vesicles in all these cases.

Three features of the arthritis are worthy of mention as bearing on the focal nature of these cases: (1) Osteoarthritic bone changes were present in all but 1 case; in this one exception there was calcification of a bursæ. (2) The recurrent attacks did not always involve all the joints originally affected and often joints which were unaffected in the original attack were involved in the recurrences. (3) The inflammation of the joints in the recurrent attacks was not as acute as in the original attack.

In other words, these cases are not true recurrences of the original gonorrheal arthritis. They are instances of arthritis due to exacerbation of seminal vesiculitis which originated during the original gonorrheal arthritis. They are complicated by osteoarthritis due to insidious action of the focal lesions.

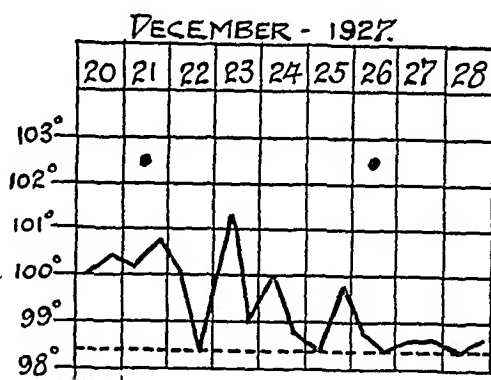
Prevention of such cases depends upon complete eradication of infection from the prostate and vesicles after acute gonorrheal arthritis.

CASES IN WHICH ARTHRITIS DEVELOPED AFTER GONORRHEA WAS APPARENTLY CURED. CASE XXII.—Three years after gonorrhea: Scant mucoid, urethral discharge; right ankle sore; few days later, left ankle sore; both ankles painful and swollen; both elbows and wrists and lumbar back painful. Ten days later arthritis had entirely subsided in all joints except ankles. Pain, swelling, tenderness and slight discoloration over tendons around external malleolus of both ankles. Roentgen ray: no pathologic bone changes. Prostate swollen; both vesicles palpable. Arthritis responded to focal treatment.

Two years later: No recurrence of arthritis; Roentgen ray: no pathologic bone changes. Prostate normal; vesicles not palpable; secretion, normal.

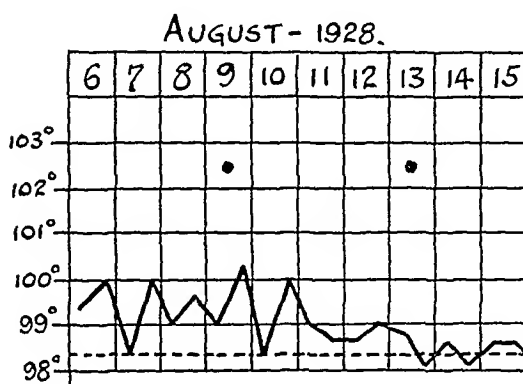
CASE XXIII.—Six years after gonorrhea: Scant mucoid, urethral discharge; left epididymitis; both heels and anterior arches of both feet painful. One week later, both ankles painful and swollen; right wrist and metacarpophalangeal joint of right index finger painful and slightly swollen; both knees painful and swollen. One month later arthritis had subsided in all joints except knees and ankles. Roentgen ray: no pathologic bone changes. Prostate slightly soft; both vesicles barely palpable. Stricture of small caliber in anterior urethra. Arthritis responded to focal treatment.

One year later; no recurrence of arthritis; x-ray, no pathological bone changes; prostate soft, vesicles not palpable; secretion, normal. Stricture dilated to 29° F.



• = INJECTION OF VESICLES

CHART II.—Temperature chart of Case XXII.



• = INJECTION OF VESICLES

CHART III.—Temperature chart of Case XXIII.

• *Comment on Cases XXII and XXIII.* The clinical features of the arthritis in these cases differ in no essential respect from those usually considered characteristic of gonorrheal arthritis. The affected joints were painful for a few days before swelling developed, several joints were involved and the arthritis finally settled in some of the larger joints.

Clinicians who believe that gonococci cause a distinct form of arthritis are very apt to diagnose such cases as gonorrheal arthritis, basing the diagnosis on the clinical course, the history of previous gonorrhea and, perhaps, the presence of Gram-negative extracellular diplococci in the prostatic secretion. Such a diagnosis is in error and may lead to the institution of inappropriate treatment which may be followed by grave consequences.

These cases are more properly called postgonorrheal arthritis and

are due to absorption from vesicles which have become the seat of postgonorrheal infection.

CASE XXIV.—One year after gonorrhea: Recurrent urethral discharge negative for gonococci; severe pain over right sacroiliac joint; surrounding tissues tender. Roentgen ray, some absorption of the cartilage of the right sacroiliac joint. Prostate slightly soft, both vesicles palpable and tender. Arthritis treated by injections of vesicles and later massage of prostate and vesicles. Four months later, no symptoms of arthritis, prostate slightly soft; vesicles barely palpable; secretion, 10 to 15 pus cells to high-power field; culture, *Staphylococcus albus*.

CASE XXV.—Three months after gonorrhea: Both shoulders and lumbar back painful in morning; pains subside somewhat during day. Prostate slightly soft; both vesicles palpable and tender; secretion, nonmotile spermatozoa, 100's pus cells. Arthritis relieved in three weeks after biweekly massage.

CASE XXVI.—Four years after gonorrhea: Both knees and both ankles painful; metacarpophalangeal joint of left thumb painful and slightly swollen. Roentgen ray: no pathologic bone changes. Prostate slightly soft; both vesicles palpable; secretion, nonmotile spermatozoa, 50 to 60 pus cells to high-power field; culture, *Micrococcus ureæ*, *Staphylococcus albus*. Massage twice weekly; arthritis relieved in three months.

Two years later: No recurrence of arthritis; prostate normal; vesicles not palpable; secretion, normal.

CASE XXVII.—Both shoulders painful at times since gonorrhea, five years ago; pains worse in past two months; no relation to movement of arms. Roentgen ray, no pathologic bone changes. Prostate soft; vesicles palpable; secretion, nonmotile spermatozoa, 100's pus cells; culture, *Staphylococcus albus*. Massage twice weekly, arthritis relieved in three months.

One year later: No recurrence of arthritis, prostate soft, vesicles barely palpable; secretion, nonmotile spermatozoa, 100's pus cells.

CASE XXVIII.—Fifty years after gonorrhea: Lower back painful and sore. Roentgen ray, some hypertrophic osteoarthritis of second and third lumbar vertebrae. Prostate slightly soft; vesicles not palpable; secretion, 50 to 60 pus cells to high-power field; culture, *Staphylococcus albus*, *Streptococcus nonhemolyticus*. Pain greatly relieved in few weeks by massage of prostate twice weekly.

One year later: Back sore at times; prostate slightly soft; vesicles not palpable; secretion, 50 to 60 pus cells to high-power field.

Comment on Cases XXV, XXVI, XXVII and XXVIII. Infection was present in the prostate and vesicles in 4 of these cases and in the prostate only in 1 of the cases. These lesions are commonly called postgonorrheal.

It is questionable whether infection in the prostate and vesicles in such cases followed actual invasion of these organs by gonococci during the course of the gonorrhea. It may be that these lesions are due to later invasion from the posterior urethra of infection following the gonorrheal posterior urethritis.

However, arthritis from such foci may be considered largely



FIG. 1.—Case XIII. Four months after gonorrheal arthritis. There are irregular areas of marked decalcification of the bones of the left knee.



FIG. 2.—Case XIII. Same as Fig. 1, but showing distention of the joint capsule of the left knee due to fluid in joint space.



FIG. 3.—Case XIII. Two years after Fig. 2. The bones of the left knee are normal.



FIG. 4.—Case XVIII. There is general decalcification of the bones of the right foot with a small spur on the under surface of the os calcis.



FIG. 5.—Case XVIII. Two years after Fig. 4. The bones of the right foot show normal bone salt content. There is no increase in the size of the spur on the under surface of the os calcis.

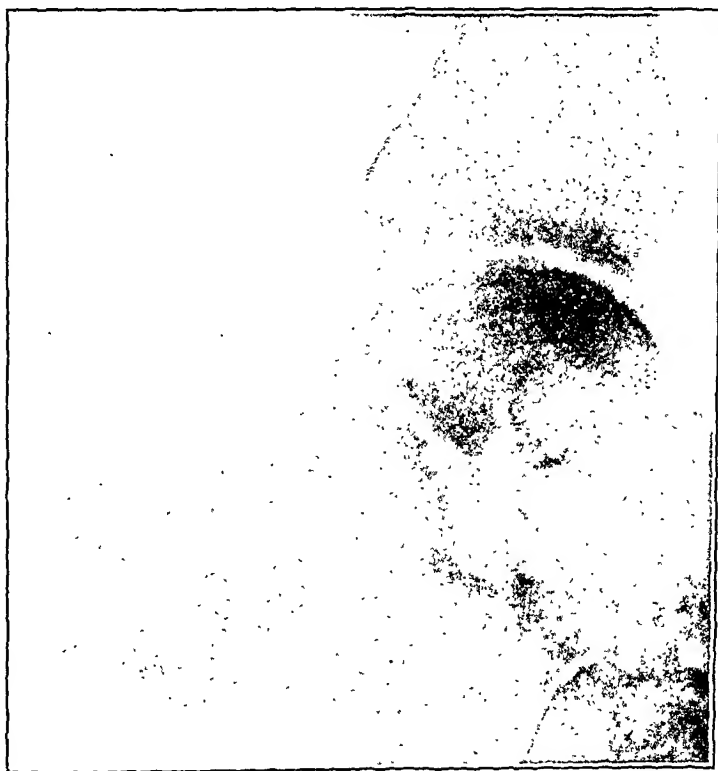


FIG. 6.—Case XIX. There is a large spur on the under surface of the right os calcis.

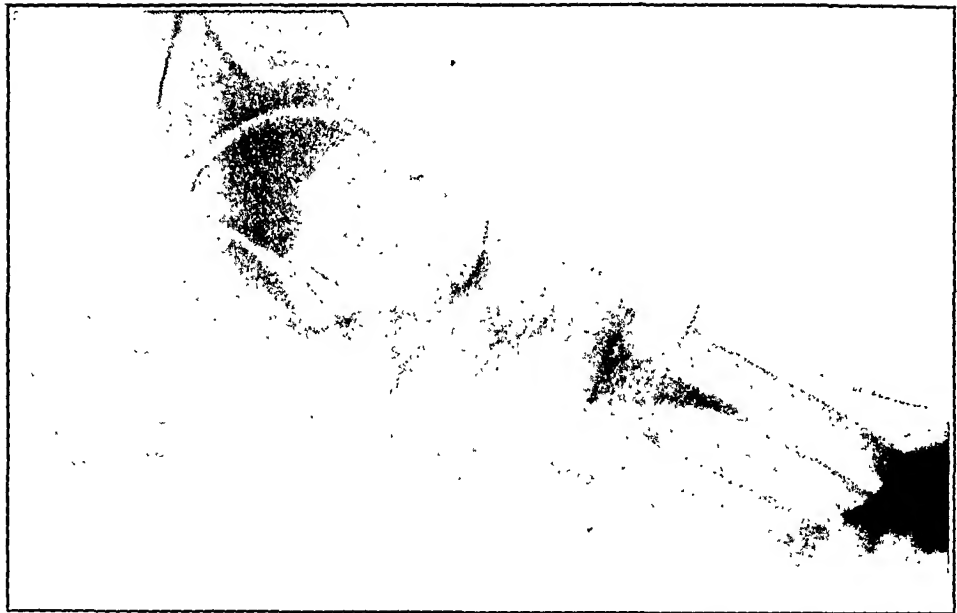


FIG. 7.—Case XIX. Two years after Fig. 6. There is no increase in the size of the spur.



FIG. 8



FIG. 9

FIG. 8.—Case XX. There is decalcification of the lower end of the fibula, the external aspect of the lower end of the tibia and the external aspect of the astragalus. There is irregularity of the external aspect of the astragalus. There is a circular area of bone infection in the superior, external aspect of the astragalus.

CASE 9.—Case XX. Ten months after Fig. 8. There is definite, although moderate, improvement in the osteoarthritis of the right ankle. There is a general increase in the bony density of the structures of the external aspect of the ankle. The external aspect of the astragalus is more regular. The chronic bone abscess cavity is slightly smaller and bone condensation has occurred around its circumference.

preventable. The means of prevention consist of reëxamination of cases of gonorrhea after apparent cure to be sure that such focal lesions do not develop.

Summary. In 2 cases of this series the clinical findings indicated that the prostate was the site of the focal infection. In Case I the prostate felt hot to rectal palpation and absorption probably occurred from the prostatic urethra. The arthritis was acute. Such cases should be recognized by routine rectal examinations in gonorrheal arthritis. In Case XXVIII the arthritis developed fifty years after gonorrhea. Infection was present in the prostate but not in the vesicles.

In all the other 26 cases the clinical evidence indicated that the seminal vesicles were the site of the focal infection. The vesicles in all cases were soft. The relationship between the arthritis and the vesiculitis is shown by the following:

In 3 cases (II, III and IV) which developed during acute gonorrhea the arthritis was comparatively mild. In these cases the vesicles were palpable but not hot.

In 8 cases (V to XII) of typical acute gonorrheal arthritis the seminal vesicles were palpable and hot. The arthritis was bilateral in 5 cases in which the vesiculitis was bilateral. The arthritis was unilateral in 2 cases in which the vesiculitis was unilateral and on the same side as the arthritis. Injection of the vesicles with Pregl's solution resulted in decline in the fever and subsidence of the acute joint inflammation in all cases. The fever and acute joint inflammation apparently depend upon the acute vesiculitis. Complete cure should include eradication of infection from the prostate and vesicles.

There were 4 cases (XIII to XVI) in which joint disability followed acute gonorrheal arthritis. In 1 case there was persistence of subacute joint inflammation, due to persistence of absorption from the vesicles after the subsidence of the acute vesiculitis. In 1 case there was osteoarthritis due to absorption from infected vesicles. In 1 case there was bony ankylosis with persistence of infection in the vesicles. In 1 case there was fibrous ankylosis with spontaneous eradication of infection from the prostate and vesicles.

In 5 cases (XVII to XXI) in which arthritis developed subsequent to apparent cure of gonorrheal arthritis there was infection in the vesicles in all cases. In 4 cases there was osteoarthritis and in 1 case there was calcification of a bursa.

There were 7 cases (XXII to XXVIII) in which arthritis developed after clinical cure of gonorrhea. In 2 of these cases the clinical features of the arthritis were such as are usually considered characteristic of gonorrheal arthritis. Infection of the vesicles was present in both cases, but the vesicles were not hot to rectal palpation. In 5 of the cases the arthritis was of the arthralgic type and associated with infection in the vesicles.

Conclusions. It would appear, then, that the clinical features of gonorrheal arthritis are due to the nature of the focal areas rather than to the nature of the gonococcus. Arthritis due to gonococcal infection of the vesicles differs from arthritis due to nongonococcal infection of the vesicles only in degree of intensity of the resulting joint lesions. The two types exhibit the same predilection of the larger joints; are both likely to involve several joints; tend to spontaneous cure of some of the involved joints with persistence in others.

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1. Stellwagen, T. C.: Gonorrheal Arthritis, Preliminary Report of a New Treatment, *J. Urol.*, 1925, 14, 661.
2. For details of this treatment, see article by Stellwagen and McCahey: *J. Urol.* 1927, 18, 1. Present Cases V, IX and XI are there Cases I, III and II respectively.

POSSIBLE ILL EFFECTS FOLLOWING INTRAVENOUS USE OF AMMONIUM ORTHO-IODOXY-BENZOATE.

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FAVORABLE results in treatment of chronic arthritis by intravenous use of ammonium ortho-iodoxy-benzoate reported by Young and Youmans,^{1,2} Smith,³ Trauba,⁴ Cottrell⁵ and many others have led to rather widespread use of this method. With the exception of that of Manace,⁶ who reports a fatality following the intravenous use of this drug, reports have been favorable. Mild reactions following administration of the drug have been common, and are apparently to be expected, but, with the exception of the case reported by Manace, no serious ill effects have been recorded.

It is the purpose of this report to bring before the profession an isolated disastrous experience with this method of treatment in order again to emphasize the fact that intravenous treatment may be not without danger. It will be seen from the cases herewith reported that the death of 1 patient and very serious illness of 3 others occurred in spite of the most careful precautions in preparation and administration of the drug solution.

Previous History of Cases.—CASE I.—Male, aged sixty-six years, was admitted to the medical department of the Multnomah County Hospital, June 22, 1927. The patient was suffering from a chronic deforming arthritis of one year's duration. All of the joints of both upper and lower extremities were involved in the process. All active foci of infection were removed. The patient was treated with different forms of medical and physical therapy for eight months without any lasting improvement.

CASE II.—Male, aged sixty-one years, admitted to the medical department of the Multnomah County Hospital, January 31, 1928. A diagnosis of chronic deforming arthritis was made. The joints of both upper extremities and the cervical spine were markedly involved, and the joints of both lower extremities involved to a lesser degree. Infected teeth and tonsils were removed, and a bilateral radical transantral sphenothmoidectomy was performed. These operative procedures plus medical and physical therapy failed to give more than slight temporary improvement over a period of three months.

CASE III.—Male, aged thirty-three years, admitted to the medical department of the Multnomah County Hospital, March 7, 1928. A sub-acute infectious arthritis involving both knee joints was diagnosed. The present attack was of ten days' duration. A chronic gonorrheal posterior urethritis and prostatitis was thought to be the source of infection, and was treated in the genitourinary department with definite but slow improvement in the affected joints.

CASE IV.—Male, aged forty-three years, had been admitted to the Multnomah County Hospital several times previous to his admittance on April 9, 1928. The patient had a chronic gonorrheal posterior urethritis and prostatitis with recurrent attacks of gonorrheal arthritis involving the larger joints of the upper and lower extremities. On previous admittances, treatments in the genitourinary department, consisting of massage, irrigations, instillations, and so forth, had relieved the patient of joint pain and stiffness. Such local treatment was being carried on with less favorable results than on previous admittances; at the same time it was suggested that the patient be given ammonium ortho-iodoxy-benzoate.

* CASE V.—Male, aged forty-six years, admitted to the Multnomah County Hospital, April, 1928. The patient gave a history of previous recurrent attacks of arthritis since 1920. The present attack was of several days' duration and involved the joints of the left lower extremity. Chronic gonorrhea, seminal vesiculitis, prostatitis and posterior urethritis, along with numerous acute gonorrheal reinfections accounted for the condition. The patient was receiving treatments in the genitourinary department at the time ammonium ortho-iodoxy-benzoate was administered.

Two different preparations of ammonium ortho-iodoxy-benzoate were administered to these patients. The following technique was used in preparation and administration of the drug: One gram of ammonium ortho-iodoxy-benzoate was dissolved in 100 cc. of normal saline solution prepared from freshly distilled water. This was injected intravenously by the gravity method, in each instance taking between twelve and fifteen minutes for administration. Fifty to 100 cc. of normal saline solution was then injected before the needle was withdrawn to prevent any possibility of local reactions at the site of injection.

The reactions observed and the results obtained, using the preparation of ammonium ortho-iodoxy-benzoate, known as oxoate (Smith, Kline & French), given intravenously, are as follows:

CASE I.—Four injections were given at four-day intervals. Reactions were noticed in about ten minutes, consisting of smarting sensation in the eyes with lachrimation, burning of the tongue, sneezing, slight salivation, increased pain and burning in the affected joints. The duration of these reactions averaged about one hour. There was no increase in temperature, pulse or respiration following administration of the drug. The results obtained were, subjectively, slight relief from pain in the joints, twenty-four to thirty-six hours after injection and objectively that a chronic conjunctivitis which the patient had had for weeks entirely disappeared after the second injection. The joints showed no changes.

CASE II.—Received four intravenous injections at four-day intervals. Reactions started in about ten minutes, consisting of smarting of the eyes and burning sensation of the tongue. Pain was greatly increased in all of the affected joints following the first two injections. The temperature which was previously normal was increased to 100° F. following the first treatment and to 99° F. following the second treatment. Following the third and fourth injections subjective relief was marked. The patient was impressed and pleased with the progress made. Objectively it was noticed that flexion and extension of the wrists and fingers and all movements of the cervical spine were actively carried out with greater freedom.

CASE III.—Received two intravenous injections at four-day intervals, showing only mild mucous membrane reactions after the first treatment. After the second treatment the patient developed a generalized toxic erythema and no further treatments were given. The joints, however, were somewhat improved.

Case IV and Case V received no treatments with "oxoate."

Another preparation of ammonium ortho-iodoxy-benzoate, manufactured by another pharmaceutical house, was then used. Cases I, II, IV and V were all given treatments the same day, using the same technique in preparation and administration of the drug as in previous treatments. The following results were noted:

CASE I.—More severe early reactions were noted than with the four previous injections. These reactions gradually became more distressing and were accompanied by abdominal cramps, vomiting, diarrhea and increased pain in the affected joints. In two and a half hours after the injection the temperature was 101° F., axilla; pulse, 124; respiration, 28. Restlessness and great anxiety was marked and headache became excruciating. The symptoms steadily increased in severity, and in spite of all efforts toward relief the patient expired eight hours after administration of the drug.

CASE II.—Again the early symptoms of burning in the eyes, mouth and nose were first noticed, as in the four previous treatments. Abdominal cramps with nausea, vomiting and watery bowel movements followed. The patient then had a severe chill, lasting forty minutes. The tempera-

ture rose to 102° F.; the pulse, 130; respiration, 30. There was extreme pain in the joints and a severe headache. These reactions lasted twelve hours. Following this, there was such a marked stomatitis and gastroenteritis that the patient was unable to eat for several days. The headache persisted for days. There was no change noted in the joints.

CASE IV.—The patient had received no previous injections. The onset of preliminary symptoms was sudden. Nausea, vomiting and headache accompanied the burning, lacrimation and salivation. There was a severe chill and the temperature increased to 101° F. The reaction lasted several hours and was followed by a marked gastroenteritis.

CASE V.—The patient had received no previous treatment. Intravenous injection of the drug was quickly followed by burning in the mouth, salivation and terrific pain in the epigastrium. There was no chill and only a slight rise in temperature. The patient suffered extreme nausea and vomiting. Headache was marked and the reaction lasted more than twelve hours.

Autopsy Record. CASE I.—(By Dr. W. C. Hunter, April 10, 1928.) This is the body of a white male (J. L.), aged sixty-six years. The body is emaciated. There is a small swelling on the lower right lid. The knee joints are enlarged and there is atrophy of the muscles of the leg and thigh.

The subcutaneous fat in the usual midline incision is 1 cm. in thickness. The cecum is seen to be distended with gas and congested. The peritoneum is smooth, moist and glistening. The small bowel is of uniform caliber. The stomach occupies the usual position. The spleen is bound down posteriorly by fibrous adhesions. The liver is at the costal margin in the right midclavicular line.

The lungs are well aerated anteriorly. The left pleural cavity is completely obliterated by old fibrous adhesions. The space occupied by the heart is increased in size. The pericardial sac contains about 50 cc. of straw-colored fluid. There is a "soldier's spot" on the anterior surface of the right ventricle about 1.5 to 2 cm. in diameter. When the heart is opened the chambers contain fluid and clotted blood. The tricuspid valve admits two fingers easily. The mitral and aortic valves admit one finger. There are no valvular changes except for a few sclerotic plaques on the mitral and aortic valves. The musculature of the left ventricle is thickened. The coronary orifices are somewhat narrowed by sclerosis but are patent. Coronal section shows the coronary vessels to be patent throughout. The aorta contains numerous pearly-white and yellowish atheromatous plaques with some evidence of linear wrinkling. There is no evidence of calcification. The esophagus is unchanged. The trachea and main arteries and main bronchi contain mucus but the mucosa is intact. The pulmonary arteries and veins, the anterior and superior venæ cavæ are all unchanged. The base of the right lung is adherent to the diaphragm. The cut surfaces of the right lung are pink in color and somewhat bloody. There is no evidence of pneumonic consolidation. There is a stellate fibrous scar in the apex of the right lobe. The left is similar to the right. The right adrenal is unchanged. There is a small amount of fatty tissue surrounding the right kidney which is slightly adherent to the capsule. The capsule of the right kidney strips readily, leaving a smooth, somewhat nodular surface beneath. The cut surfaces pout on approximation. The normal markings are somewhat distorted. There is a decrease in the cortex and an increased amount of fat in the pelvis. The fatty tissue around the kidneys is gelatinous and rich in fluid. The vessels of the kidney are prominent when cut

across. The left kidney is similar to the right. The wall of the gall bladder is somewhat thickened, raised, white in color and contains yellowish bile. The common duct, portal vein and its tributaries are unchanged. The capsule of the liver is smooth, with a slight increase in the fibrous elements. The liver cuts with increased resistance. The cut surfaces show slight mottling. The cut surfaces of the spleen are dark red in color. The pulp scrapes away easily, leaving the Malpighian corpuscles and an increased amount of connective tissue standing out prominently. Grossly the pancreas is unchanged. When the stomach is opened there is a small amount of undigested food material found. The mucosa is covered with a thick layer of grayish mucous material. The mucosa is bright red in color and densely studded with petechial hemorrhages. When the large bowel is opened the mucosa is markedly hyperemic and congested. This also extends into the ileum. The prostate is not increased in size.

When the calvarium is removed the dura is thickened and the pia arachnoid stands high above the convolutions with fluid beneath. When the brain is removed all the cranial fossæ are filled with a yellowish fluid. In several areas over the vertex the pia arachnoid shows small stellate scars. Sectioning the brain shows the ventricles to be filled with fluid. The choroid plexus is intact. There are no areas of hemorrhage or softening. There are, however, petechial hemorrhages in the medullary portion. The blood is a cherry-red color.

Anatomic Diagnosis. Marked edema of the brain; dilatation of the right heart; congestion of the lungs; marked hyperemia and congestion of the mucosa of the colon and part of the ileum; marked congestion of the mucosa of the stomach; chronic diffuse nephritis; cloudy swelling of parenchymatous organs; chronic obliterative fibrous pleuritis, bilateral; fibrous splenitis; marked contractures of the hands; swelling of the knee joints.

Summary. Death appears to be the result of an overwhelming toxemia.

Pharmacologic Report. Samples of the two preparations used in our treatment of the above cases were submitted to Dr. Harold B. Meyers, Professor of Pharmacology, Department of Medicine, University of Oregon, for analysis. His results are expressed in the following communication:

"We wish to acknowledge receipt of the two preparations of ammonium ortho-iodoxy-benzoate hereinafter referred to as preparation 'A' and preparation 'B,' the latter having caused the toxic reactions described by you.

"The hydrogen-ion concentrations of 1 per cent solutions of both salts shows that preparation 'B' has a pH of 5.35 and preparation 'A' a pH of 5.75. The slightly greater acidity of preparation 'B' might play some part in the toxic reaction. It is unlikely that the difference in hydrogen-ion concentration would account for more than a minor part of the difference in toxicity of the two preparations; considering that 1 gram was the total amount of drug injected, and that it was given slowly as 1 per cent solution.

"Experimental animals injected intravenously with 1 per cent solutions of preparations 'A' and 'B' in isotonic saline with buffer salts to equalize difference in hydrogen-ion concentrations, show that preparation 'B' has a much more pronounced toxic effect than

preparation 'A.' These salts were injected in 1 per cent solution at the rate advised for human administration in dosage of 14.3 mg. per kilo, which is the concentration for an adult of approximately 150 pounds' weight. The animal injected with preparation 'B' stopped breathing, lay apparently lifeless and had very feeble heart action for some time following injection. Symptoms indicating possible fatal results occurred before the injection was completed.

"Some have asked if the iodine content of the salt might account for the toxic reaction. It is improbable that the iodine liberated as iodine from the salt could account for the toxic results because the minimal fatal dose of iodine is larger than the total amount of iodine contained in the salt. It is my belief that the toxicity is due probably to an intermediary substance prepared in the process of manufacture, such as an iodoso compound, which is relatively highly toxic."

Summary. Five cases of different types of arthritis were treated with two brands of ammonium ortho-iodoxy-benzoate intravenously. With the first preparation, oxoate, 10 injections were given with some, alleviation of symptoms and no untoward results. One injection of a second preparation given to each of 3 of these cases previously treated produced severe toxic symptom in 2 and death in the third. A fourth individual suffering from gonorrheal arthritis who had had no previous injections was given one dose of the second preparation with toxic reaction.

Conclusions. Our clinical experience with these four simultaneous reactions speaks against the assumption that an individual idiosyncrasy either to iodine or salicylates is probable. Furthermore, animal experimentation with two different preparations showed a difference in toxicity. The technique of administration was identical in each instance. It has been suggested and is, in our opinion, quite likely that, either in manufacture, administration or decomposition of the drug in the blood stream, there was set free an intermediary toxic product which was responsible for the injurious effects observed.

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INOCULATION MALARIA: SEXUAL AND ASEQUAL STRAINS.

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THE practical value of an asexual strain of malaria in the treatment of general paralysis as has already been pointed out, lies in the fact that "(a) it eliminates the possibility of the transmission of malaria to other members of the community; (b) it precludes the occurrence of malarial relapse following adequate quinin administration."¹ In a single strain of benign tertian malaria continuously in use since June, 1923, in over 350 patients we have so far failed to find any gametocytes in peripheral blood smears.

The question immediately arises as to whether a sexual strain of benign tertian malaria would lose its capacity to develop gametocytes upon continuous artificial human passage. The present report deals with this problem.

A strain of malaria was obtained in which gametocytes were present.* This strain was first used on May 9, 1928 and up to August 8, 1929, 123 patients have been inoculated—88 females and 35 males. As a rule such inoculations were made intravenously, occasionally subcutaneously. The malarial course paralleled that induced by our former "asexual"† strain and the therapeutic results in general paralysis were identical.

Daily smears from all patients were examined from the first elevation of temperature to its cessation. In all, over 1700 Wright-stained slides were studied microscopically.

In general most of the slides contained malarial parasites (in varying numbers). The important point under consideration is the comparative presence and absence of gametocytes.

A striking difference is to be noted between the two groups as regards the per cent of slides with parasites showing gametocytes. In order to bring this point out more clearly, averages are presented in Table I.

TABLE I.—GAMETOCYTES IN FEMALE PATIENTS.

	Average per cent of slides with parasites showing gametocytes.	Actual number of cases showing no gametocytes.
Group 1—Case Nos. 1 to 44	69	0
(May 9 to November 2, 1928.)		
Group 2—Case Nos. 45 to 89	16	13
(November 2, 1928 to August 8, 1929.)		
Reduction	53	

* Thanks are due Dr. C. O. Cheney, Superintendent of the Hudson River State Hospital, Poughkeepsie, N. Y., for his kind coöperation in securing this strain.

† Asexuality will have to be finally determined by testing transmission by mosquitos.

Table I is arbitrarily divided into two equal groups: Case Nos. 1 to 44 constituting the first group and Case Nos. 45 to 88 constituting the second group. In point of time the first group was inoculated during a period of seven months. The second group was inoculated during the succeeding nine months.

Thus, compared with the first group there has been a reduction in the second group of 53 per cent in the average per cent of slides with parasites showing gametocytes. Furthermore, in the first group of 44 patients there was not a single patient whose slides showed parasites with a complete absence of gametocytes. Contrast this with the second group of 44 patients where there were 13 patients whose slides with parasites contained absolutely no gametocytes. In other words, gametocytes failed to appear in approximately one-third of the patients in the second group.

These findings point definitely to the fact that in female patients the sexual strain of malaria is rapidly losing its capacity to produce sexual forms. How many more passages will be required before the sexual strain becomes entirely asexual is a matter of speculation but the investigation is being continued. Again it should be emphasized that clinically no differences could be observed between patients having sexual forms of the malarial parasite and those having only asexual forms.

Consider now the results obtained with male patients. These are presented in Table II where an arbitrary division has been made on approximately the same time basis as in the female patients, that is, all male patients, Case Nos. 101 to 114 inoculated during the first seven months fall in the first group, while Case Nos. 115 to 135 fall in the second group during the subsequent nine months.

TABLE II.—GAMETOCYTES IN MALE PATIENTS.

	Average per cent of slides with parasites showing gametocytes.	Actual number of cases showing no gametocytes.
Group 1—Case Nos. 101 to 114	73	0
(May 9 to October 23, 1928.)		
Group 2—Case Nos. 115 to 135	38	1
(November 9, 1928 to August 3, 1929.)		
Reduction	35	

From Table II it will be seen that in the first group 73 per cent of patients having slides with parasites showed the presence of gametocytes, while in the second group the corresponding figure was 38 per cent. This represents a reduction of 35 per cent. It will be remembered that in female patients the reduction for the same period of time was greater, namely, 50 per cent. No patient in the first male group and only one patient in the second male group had a total absence of gametocytes when malarial parasites were present. Again it will be recalled that 13 female patients or approximately one-third of the second group had a total absence of gametocytes.

The obvious inference from these findings is that while there is some tendency for the sexual strain to lose its capacity to produce gametocytes in male patients, this tendency is not nearly so striking as in female patients. Human sex differences apparently exert an unmistakable influence upon the life cycle of the malarial parasite. An adequate explanation of this curious phenomenon is still wanting.

It was stated at the outset that the "asexual" strain of malaria is still being used therapeutically. During the progress of the present investigation the inoculation of the 88 female and 35 male patients with a sexual strain of malaria was paralleled by the inoculation of 36 patients with our older "asexual" strain of malaria. Daily examination of all stained smears in the latter patients failed at any time to reveal the presence of gametocytes. This corroborates our previous findings.¹

Biologically it appears, then, that a sexual strain of malaria upon repeated human passage loses its capacity to produce sexual forms. Such an adaptation might well be anticipated in the light of our knowledge of parasitism. The malarial parasite must have sexual forms to complete its life cycle in mosquitos but gametocytes are unnecessary for further propagation in *homo sapiens* exclusively. Clinically this biological adaptation possesses certain advantages to which reference has already been made.¹

Therapeutically there is practically no difference between the "asexual" and sexual strains of malaria. Thus Hinsie² working at the Psychiatric Institute, found that 32 per cent of female patients with general paralysis showed improvement when inoculated with the "asexual" strain of malaria. In the series of cases here described many female patients were nonlucetic but among the general paralytics 27 per cent showed improvement when inoculated with the sexual strain of malaria. Again in male general paralytics, Bunker and Kirby³ found that 55 per cent improved when inoculated with the "asexual" strain of malaria, while in our series of male general paralytics 54 per cent improved when inoculated with the sexual strain of malaria. Obviously the slight discrepancy in favor of the "asexual" strain falls well within experimental error and the conclusion remains that sexual and "asexual" strains of malaria follow the same clinical course.

Summary. 1. The malarial course and therapeutic results in 123 patients (88 females and 35 males) inoculated with a sexual strain were identical with those noted in over 350 patients inoculated with an "asexual" strain of malaria.

2. After seven months the sexual strain of malaria began to lose its capacity to produce gametocytes. During the succeeding nine months this was found to be much more striking in female than in male patients. Approximately one-third of all the female patients having malarial parasites failed to reveal the presence of any sexual forms of the plasmodium.

3. The sexual strain of malaria becomes biologically adapted to its host upon repeated human passage, as evidenced by its increasing failure to produce gametocytes.

NOTE.—Particular acknowledgment is due Mr. Peter Cohen for his active assistance in this investigation. It is always a privilege to express appreciation of the interest and coöperation of Dr. George H. Kirby, Director of the New York State Psychiatric Institute and Hospital, the present members of the Clinical Staff, Drs. L. E. Hinsie and Joseph R. Blalock, and the former members, Drs. C. O. Fiertz and Samuel Parker.

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THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG.

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IN 1912, after an extensive review of the literature, Adler¹ collected 374 cases of carcinoma of the lung. He noted then, that "on one point however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of disease." Since then there has appeared a considerable literature attesting to the increased frequency of this condition. The etiologic, clinical and pathologic aspects of primary carcinoma of the lung have received adequate attention, but not enough emphasis has been placed on the question of incidence. This paper will attempt to correlate evidence pertaining to the frequency of primary carcinoma of the lung, and to present new evidence from the Boston City Hospital.

Some idea of the more frequent occurrence of primary carcinoma of the lung today, may be gained by comparing the older reports with those of the present. Reinhard² collected 5 cases among 8716 autopsies in Dresden from 1852 to 1876, and Fuchs³ found 8 cases among 12,307 autopsies in Munich from 1854 to 1885. More recently, Symmers,⁴ at Bellevue Hospital, saw 8 cases from July, 1919, to December, 1920; and Moses⁵ reported 3 cases occurring between February 12 and June 1, 1924, at the Kings County Hospital. Ferenczy and Matolcsy,⁶ in a review of the autopsy material at the Pathological Institute, Vienna, found only one case in 1896, and 32 cases in 1924. From 1910 to 1918 there were 4 cases of primary

carcinoma of the lung at the Boston City Hospital among 964 adult autopsies (0.42 per cent), and this increased in the years 1919 to 1928 to 17 cases among 2040 autopsies (0.83 per cent).

For valid comparison of the incidence of this condition definite criteria for diagnosis and statistical report should be established. Of these, the following have been modified from Weller:⁷

1. An autopsy must have been performed.
2. The carcinomatous nature must have been verified microscopically.
3. There must be no reasonable doubt that the neoplasm was not a primary growth.
4. Percentage should be calculated on the basis of total adult necropsies.

Although gross section is often sufficient for a pathologic diagnosis of primary carcinoma of the lung, in an occasional instance histologic examination is necessary to differentiate other noncarcinomatous intrathoracic neoplasms—lymphosarcoma, fibrosarcoma, lymphoblastoma. Where there is no microscopic examination, it may be reasonable to believe that the condition is not carcinoma, and these cases should not be included in statistical reports. Also, the primary lesion is frequently allocated to the lung in many instances in which that organ is involved in a generalized carcinomatosis. For accurate statistical data, if there is any reasonable suspicion that the primary growth was not in the lung, the case should be excluded. It is evident also, that the percentage incidence will be effected by the age group of patients undergoing autopsy examination. In a general hospital, with a large active pediatric service, where in the autopsy material there is fair representation of the noncarcinomatous age group, the incidence if based on total autopsies, will be lower than in a hospital with few pediatric cases. For purposes of comparison, therefore, a uniform method of arriving at percentage incidence should be established. In the author's series, following the example of Berblinger⁸ and Wahl,⁹ the percentage incidence is based on the number of autopsies of patients over twenty years of age, twenty being taken arbitrarily as the lowest age limit of carcinoma.

The major statistical studies of primary carcinoma of the lung have been made on the Continent. Only a few have appeared in the English and American journals. Although with one or two exceptions all authors are convinced that this affection is more frequent now than it was a generation ago, a satisfactory comparison of the percentage incidence from the statistics cited presents many difficulties. Some authors include all intrathoracic new growths; others only carcinomas. Some authors form percentage figures on the basis of total necropsies, irrespective of age; others on total adult autopsies, that is, patients over twenty years of age. Some groups are too small to permit satisfactory conclusions; in others,

insufficient data are given; and in a few reports histologic examination has not been performed or no statement is made that it has been performed.

TABLE I.—A SUMMATION OF THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG, AS GIVEN BY VARIOUS AUTHORS.*

Year.	Summated from authors who give total autopsies, total number of all cancers and total primary lung cancers.			Summated from authors who give total number of autopsies and total number of lung cancers.			Summated from authors who give total number of all cancers and total number of lung cancers.		
	Total autopsies.	Total cancers.	Total cancers to total autopsies, per cent.	Total autopsies.	Total lung cancers.	Total lung cancers to total autopsies, per cent.	Total cancers.	Total lung cancers.	Total lung cancers to total cancers, per cent.
To 1899	27,126	2201	8.11	63,633	89	0.14	2201	32	1.45
1900-1904	16,523	1379	8.34	21,818	45	0.21	1614	41	2.54
1905-1909	22,862	2360	10.32	27,268	95	0.35	2595	91	3.50
1910-1914	31,229	3246	10.39	37,580	165	0.44	3560	161	4.52
1915-1919	43,524	4437	10.19	49,244	213	0.43	4857	209	4.30
1920-1924	38,458	4788	12.47	43,379	354	0.81	5204	344	6.61
1925-1928	6,929	1069	15.43	6,929	94	1.36	1069	94	8.79
1910-1919	74,753	7683	10.27	86,824	378	0.44	8417	370	4.39
1920-1928	45,387	5857	12.90	50,308	448	0.89	6273	438	6.98

* Some investigators omit the total number of autopsies, others do not give the total number of cancers. This incompleteness necessitates the tabular form presented.

Recognizing these sources of error in computing a satisfactory comparative incidence, Table I was constructed. It represents a summation of the reports of Berblinger,⁸ Breckwoldt,¹⁰ Fuchs,³ Hanf,¹¹ Holzer,¹² Katz,¹³ Kikuth,¹⁴ McCrae,¹⁵ Marchesani,¹⁶ Materna,¹⁷ Moise,¹⁸ Pässler,¹⁹ Reinhard,² Sonnenfeld,²⁰ Staehelin,²¹ Wahl,⁹ Wolf²² and the author's series from the Boston City Hospital. The reports of Bonser,²³ Duguid²⁴ and Simpson,²⁵ were not included since these authors considered all intrathoracic tumors. The data of Seyfarth²⁶ were excluded because of incompleteness. Last were excluded the statistics (Table II) of Barron,²⁷ Biberfeld,²⁸ Brandt,²⁹ Briesse,³⁰ Eichengrün and Esser,³¹ Ferenczy and Matolcsy,⁶ Fried,³² Grove and Kramer,³³ Klotz,³⁴ Lavrinovich³⁵ and von Wiczkowski,³⁶ because they do not give yearly frequency or because they could not be represented conveniently in the year groups of Table I. With the exception of Bonser, however, all of the authors whose work has not been included in Table I, recognize an increase in lung cancer. This table shows a steady rise in the relation of primary carcinoma of the lung to total autopsies and to all carcinomas.

TABLE II.—THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG.*

Author.	Year.	Total autopsies.	Cancers.		Primary lung cancers.		
			Total No.	Autopsies, per cent.	Total No.	Autopsies, per cent.	All cancers, per cent.
Barron . .	1899-1911	1,332	0		
Briese . .	1898-1916	12,971	1287	9.92	60	0.46	4.7
Wiczowski . .	To 1913	58,497	125	0.21	
Lavrinovich . .	1905-1915	16,047	1649	10.28	61	0.38	3.7
Klotz . .	1910-1920	1,000	5	0.50	
Ferency and Matolesy . .	1896-1925	62,802	6791	10.80	282	0.45	4.1
Biberfeld . .	1897-1925	36,428	207	0.57	
Barron . .	1912-1918	2,026	4	0.19	
Barron . .	1919-1921	1,003	9	0.89	
Brandt . .	1901-1925	13,179	1825	13.83	108	0.82	5.9
Eichengrün and Esser . .	1902-1926	13,318	932	7.07	68	0.51	7.3
Fried . .	1915-1925	1,400	136	9.71	5	0.35	3.6
Grove and Kramer . .	1917-1924	3,659	21	0.57	
Klotz . .	1920-1927	1,900	19	1.00	

* These statistics are not included in Table I.

Reports from the Dresden City Hospital are available which give the incidence over a period of fifty years (Table III).

TABLE III.—PRIMARY CARCINOMA OF THE LUNG AT THE DRESDEN CITY HOSPITAL.

Author.	Year.	Total autopsies.	Autopsies which were lung cancers, per cent.	All cancers which were lung cancers, per cent.
Reinhard ² . .	1852-1876	8,716	0.057	0.92
Wolf ²² . . .	1877-1894	11,400	0.351	
Rau ³⁷ . . .	1909-1914	4,905	0.306	2.72
	1914-1919	5,488	0.490	4.66

The relation of primary carcinoma of the lung to all cancers rose from 0.9 to 4.66 per cent in the years 1852 to 1919, a considerable increase.

In England, Rolleston and Trevor³⁸ reviewing 3983 autopsies at St. George's Hospital from January 1, 1890, to July 8, 1902, found 8 instances of neoplasm of the lung, of which only 2 were carcinomas. A similar low incidence is reported by Playfair and Wakeley³⁹ from King's College Hospital. Among 3183 autopsies from 1901 to 1923, there were only 4 cases of primary carcinoma of the lung in which there was no element of doubt in the diagnosis, an incidence of 0.1 per cent. More recently statistics from England have been very much higher, among the highest in the literature, probably

because all intrathoracic new growths are included in the surveys. Duguid²⁴ and Simpson²⁵ have each noted a substantial increase in intrathoracic malignancy, and each is satisfied that there is a true increase in carcinoma of the lung. Moreover, Simpson's figures from the London Hospital indicate that there was no associated increase in the total carcinomas from all parts of the body.

Bonser's analysis of autopsied cases at the Leed's General Infirmary during the years 1891-1927 showed no increase in intrathoracic cancer, and this in a hospital where 83.6 per cent of all deaths in thirty-seven years have undergone autopsy examination. However, of the 172 cases of intrathoracic malignancy which Bonser found, only 60 cases or 35 per cent were examined histologically. Of these 60 cases, 24 were oat-cell sarcoma of the mediastinum, 6 were small round-cell sarcomas, and 2 were Hodgkin's sarcoma. It is conceivable that the yearly distribution of the noncarcinomatous intrathoracic neoplasms in Bonser's series obscures an actual increase in the frequency of true carcinoma.

Both Bonser and Simpson are of the opinion that intrathoracic new growths are usually carcinomatous. Simpson states that Turnbull "has for many years held the view that primary malignant disease of the lungs and bronchi are nearly all carcinomata, and that the so-called 'oat-celled sarcomata' (also termed lymphosarcomata, mediastinal sarcomata, lymphosarcomata of the mediastinum) are in reality true carcinomata." Barnard⁴⁰ also concludes that the oat-cell sarcoma of the posterior mediastinum is a medullary carcinoma of the bronchus. Nevertheless, until this view is generally accepted, it is well to include in a study of carcinoma of the lung, only those conditions which are universally recognized as carcinomatous.

In spite of the rather widespread belief that primary carcinoma of the lung is a rare condition, in the author's series of 314 cancer deaths, the lung stands fifth in the order of involvement. Kikuth,¹⁴ studying postmortem sections at the Hamburg Eppendorf Hospital in 1923, found that the lung was the organ second most frequently affected by carcinoma. A similar study by Eichengrün and Esser³¹ of 932 cancer deaths or 7 per cent of all autopsies from 1902 to 1926, placed carcinoma of the lung fifth in frequency, and Briesse,³⁰ studying 1287 cancer cases comprising 10 per cent of autopsies from 1898 to 1916, found it the sixth most frequent cancer.

In reviewing the autopsy protocols at the Boston City Hospital the criteria previously noted were rigidly adhered to. The reports are full and complete, and all cases have had microscopic examination. Moreover, there has been no change in the supervisory staff. Dr. Frank B. Mallory, to whom the author is indebted for the use of this material, has been in active charge of the Department of Pathology during the entire period considered. In doubtful cases the histologic sections were reexamined.

From 1910 to 1928 there were 3004 adult autopsies, of which 314 or

10.4 per cent were cancer cases. Primary carcinoma of the lung occurred twenty-one times or 0.70 per cent of all adult autopsies, and 6.69 per cent of all cancers (Table IV). Other intrathoracic tumors observed were three fibrosarcomas, one endothelioblastoma, and one mesothelioma. Lymphoblastomas were not included. In the period 1925 to 1928, the percentage relation of all cancers to total autopsies increased from 10.29 to 12.35 (an increase of 20 per cent). Coincidentally, the percentage relation of primary carcinoma of the lung to total autopsies rose from 0.57 to 1.03 (an increase of 81 per cent); and the percentage relation of primary carcinoma of the lung to all cancers rose from 5.55 to 8.28 (an increase of 49 per cent). The increase in primary carcinoma of the lung is evidently much greater than the increase in all cancers. The group is of course too small to indicate an absolute increase in lung carcinoma, but the results are highly suggestive of a real rise in incidence.

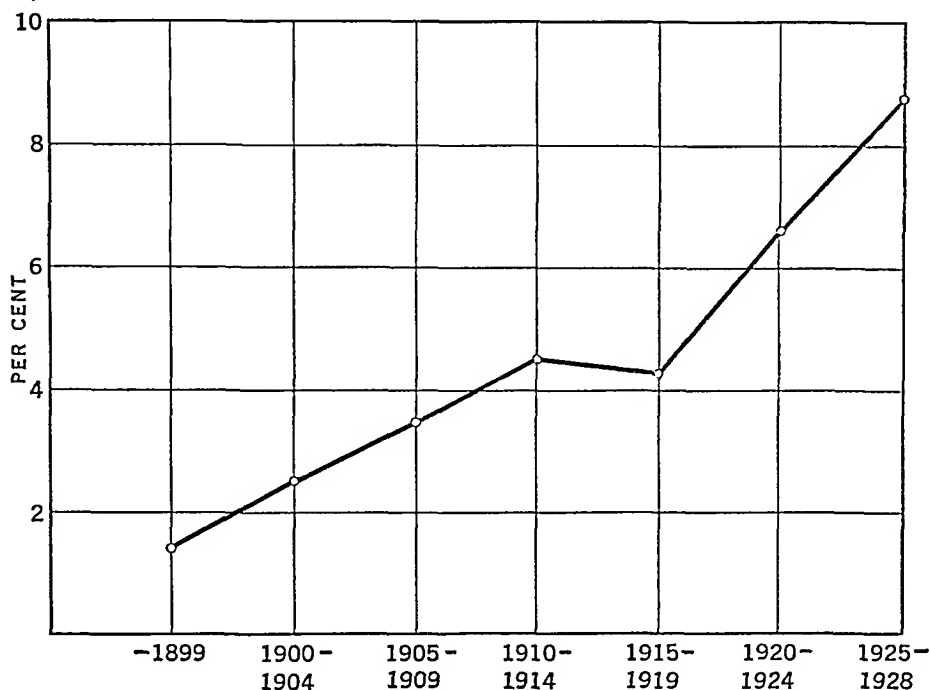
TABLE IV.—PRIMARY CARCINOMA OF THE LUNG AT THE BOSTON CITY HOSPITAL.

Year.	Number of adult autopsies.	Carcinomas.		Primary lung carcinomas.		
		Total number.	Autopsies, per cent.	Total number.	Autopsies, per cent.	All carcinomas, per cent.
1910-1914 . .	438	34	7.76	2	0.46	5.88
1915-1919 . .	526	45	8.55	2	0.38	4.44
1920-1924 . .	874	90	10.29	5	0.57	5.55
1925-1928 . .	1166	145	12.35	12	1.03	8.28
1910-1928 . .	3004	314	10.45	21	0.70	6.69

There is evidently much difference of opinion over the question whether this increase, noted by practically all observers, is a real, absolute increase, peculiar to the lung, or only relative to and coincidental with a general increase in systemic cancer. Simpson,²⁵ Duguid,²⁴ Wahl,⁹ and Rau,³⁷ are convinced that this increase is a real one, while Lichty,⁴¹ Eichengrün and Esser,³¹ Fried,⁴² and Marchesani¹⁶ feel that the greater frequency is only relative and associated with an increase in carcinoma cases. If the increase in primary carcinoma of the lung were due to the increase in all cancers, then over a period of years the relationship between these two factors would be constant, and the curve showing the percentage relation of lung cancers to all cancers would be represented by a horizontal line. That this is not so is shown by the graph (Chart I) drawn from the statistics in Table I. The trend of the curve is definitely up. This chart does not involve the age group of autopsy material since only carcinomas are considered, and so one source of error, infant autopsies, is eliminated. The conclusion must be drawn that in recent years there has been a real, absolute increase in the frequency of primary carcinoma of the lung.

Certain factors have been presented which might contribute

towards this increase. That clinical and pathologic acumen is greater today than it was a generation ago cannot be doubted. More cases are diagnosed both pre- and postmortem. Also, as Wells⁴³ rightly observes, the tremendous advances in communication and modes of transportation make modern diagnostic facilities available to the most secluded hamlet. As a result, more and more patients with bizarre symptoms come to hospitals for observation, and especially for roentgenologic examination. Then too, in hospitals where interns secure permission for necropsy, greater efforts are made to obtain consent for the examination of interesting



The percentage relation of primary carcinoma of the lung to all carcinomas.
Drawn from the statistics in Table I.

cases. But there seems to be no reason why these considerations should be effective only with regard to carcinoma of the lung. They apply with equal force to carcinoma of any organ, and for that matter to any puzzling disease that presents diagnostic difficulties. If these factors alter the postmortem frequency of carcinoma of the lung, they will alter to the same degree the postmortem frequency of all cancers, and the percentage relationship therefore, will not be influenced.

Conclusions. 1. The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute.

2. Combined statistics show that primary carcinoma of the lung at autopsy from 1910 to 1919 comprised 0.44 per cent of autopsies, and 4.39 per cent of all cancers. Since 1920, primary carcinoma of the lung at autopsy comprised 0.89 per cent of autopsies and 6.98 per cent of all cancers.

3. Primary carcinoma of the lung is not as rare as was formerly believed. Because of its increased frequency, the clinician should give this affection serious consideration in differential diagnosis in patients of the carcinomatous age presenting puzzling lung symptoms and signs. An early diagnosis will permit accurate prognosis, and in selected cases, perhaps, surgical therapy.

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TERTIARY SYPHILIS OF THE LIVER SIMULATING BANTI'S SYNDROME.

WITH REPORT OF A CASE AND REVIEW OF THE LITERATURE.

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THE question of whether the clinical-pathologic complex described some thirty-five years ago by Banti is really founded upon pathologic changes peculiar to itself, and is thus entitled to the designation "Banti's disease," or whether it is simply a superficial variant, or result, of some separate and distinct pathologic entity, and therefore merits a status no more definite than that of a syndrome, remains unanswered. A further problem, or perhaps the primary problem, concerns the etiology of this syndrome, about which there is no agreement whatsoever. At one extreme we have Banti's original assertion that it is a disease *sui generis*, and at the other the declaration of Norris, Symmers and Shapiro¹¹⁴ that the syndrome is nothing more than one of the manifestations of tertiary syphilis. The interjacent territory is occupied by those—for example, Neuberg⁵⁶—who believe that any one of many infectious or "toxic" agents, operating in the portal system, may reproduce all the essential clinical and pathologic manifestations of the Banti syndrome.

It is not the intent of this paper to enter into this controversy, nor to recite its pros and cons. For a comprehensive discussion of the problem the reader is referred to the papers of Wentworth,¹²⁴ who brings the subject up to 1901 and appends a long bibliography, Stein,¹²¹ Leon-Kindberg,⁴³ whose bibliography contains 135 references, Krull,⁴¹ Moschcowitz,¹¹⁰ and Carr.⁸⁹ Moschcowitz's critique, in particular, is penetrating and illuminating. Suffice it for our purpose to say that even the most casual examination of the literature leads to the conviction that the syndrome often appears to manifest itself *ab initio* as an independent process, whereas not infrequently it is found to be reproduced perfectly by tertiary syphilis of the liver. If it has other apparent origins they are not of sufficiently frequent occurrence, or sufficiently unequivocal, to demand serious attention. Certain it is that in the present state of our knowledge it would be better to let the question of etiology remain *sub judice*, employing meanwhile the designation "Banti's syndrome" in preference to "Banti's disease."

Ex cathedra pronouncements, such as that of Norris, Symmers and Shapiro,¹¹⁴ that Banti's syndrome is always caused by syphilis, serve chiefly to obfuscate the problem. Those who take the trouble to look will find in the records a great many cases of Banti's syndrome in which it was established beyond reasonable doubt that syphilis played no part whatsoever in the etiology. The authors would have done well to mend their own fences; they forget that the clinical aspects of Banti's syndrome demand some attention. The statement of Symmers, Gettler and Johnson⁷⁶ that their 6 cases, or at least 3 of them (which 3 not indicated), were diagnosed clinically as Banti's syndrome, would carry more conviction if the cases had been described in sufficient detail to enable the reader to form his own opinion (see Tables II and III, and discussion).

It is the purpose of this paper to report a case of tertiary syphilis of the liver which manifested itself as Banti's syndrome in the terminal stages, and to collect from the literature as many similar cases as possible. As far as I can discover, a comprehensive review and critical analysis of these cases from this point of view has never been published.

Report of Case. History.—The patient was born in 1901 and was considered a perfectly healthy and robust child until 1912, at which time she suffered a severe attack of scarlet fever. Thereafter, she never regained her former vigor and good health. She remembered being told by her school teacher that her color was "bad." In 1915 she had measles, recovery from which was interrupted by an upper respiratory infection with fever, following exposure to cold and wet. After this she was neither better nor worse, but remained in a state of chronic ill-health characterized by weakness, secondary anemia, and intermittent attacks of very mild jaundice. The last-named symptom made its first appearance shortly after her scarlet fever. The patient did not begin to menstruate until she was twenty years of age, and never had more than three menstrual periods a year, always with scanty flow.

Throughout the summer of 1924 the patient had an almost continuous fever of unknown origin, reaching frequently as high as 103° F. She felt unusually weak and "nervous" during this period, but there were no definite localizing symptoms. In the fall of 1924 she was examined by a physician who told her that she had an enlarged spleen, and she remembered that for a year or more prior to that time she had noticed soreness in the splenic region intermittently, especially after exertion. This symptom continued without change throughout the rest of her illness. Some time in the winter of 1924-1925 a dull ache appeared in the right leg and thigh, increasing gradually in intensity until it interfered with sleep. Two weeks later a similar ache made its appearance in the left arm, and increased slowly. Because these aching pains were never aggravated by movement of the joints the patient felt that they originated in the bones themselves. Finally they spread to most of the long bones, and although they never became extremely severe, they continued to annoy her intermittently ever afterward.

Early in September, 1928, the patient passed a tarry stool, and found herself unusually weak the next day; there was no coincidental abdominal pain. Aside from this single experience, there was no history of hemorrhage from the gastrointestinal tract.

About September 1, 1928, while holding a trivial weight in her left hand, meanwhile keeping her left arm braced against her body, she was reaching upward with her right arm when she felt and heard something snap in her left arm and immediately experienced an excruciating pain just above the left elbow. The next day the left arm was swollen and slightly warmer than its fellow, and it remained swollen and painful until she was admitted to the hospital a month later.

There was no family history of tuberculosis or jaundice. The patient's parents and two brothers were alive and well; two brothers and a sister died in infancy from unknown causes. She was married in 1922, but had never been pregnant, a circumstance which she ascribed to the fact that her uterus was "underdeveloped." She denied venereal infection.

Physical Examination. Patient was admitted to the University Hospital, September 27, 1928, complaining of pain in the left arm, and general weakness. She was a poorly nourished, fragile little woman, aged twenty-seven years, pale and slightly jaundiced. The left arm, elbow and upper fore-arm were much swollen. The shoulder and elbow joints were unaffected, but just proximal to the elbow there was an area of extreme tenderness, and all attempts at active or passive movement of the arm resulted in excruciating pain in this area.

There was a normal growth of hair on the head, in the axillæ, and over the pubes. The skull was not remarkable. The nose was normal. Hearing and vision were unimpaired. The scleræ were slightly icteric. The corneæ were absolutely clear, the pupils reacted satisfactorily to light and in accommodation, and the fundi were negative to ophthalmoscopic examination. All the teeth had been removed. The tongue, pharynx and tonsils were not abnormal. A few lymph nodes were palpable in the cervical, inguinal, and femoral groups, but the character and extent of the enlargement were insignificant.

Examination of the lungs showed nothing except a few râles and a small amount of fluid at both bases. The heart was moderately dilated; the peripheral arterial pulse was not of large volume, but was distinctly celer in character; and there was an endocardial (hemic) systolic murmur over the conus arteriosus—changes which were quite in keeping with the long-standing anemia. There were no signs of disease of the aorta. The arterial blood pressure was 106/56 mm. Hg.

The abdomen was somewhat enlarged, and a few slightly dilated veins were visible along either side. There was a moderate amount of ascites.

The spleen was greatly enlarged, reaching to the level of the umbilicus and extending several centimeters to the right of the midline; its surface was smooth, its consistency firm, and its edge moderately rounded; it was slightly tender to pressure. The liver was not only not enlarged, but distinctly smaller than normal, so that none of its physical characters could be made out.

There was some edema below the knees, none elsewhere. No abnormal neurological signs were discovered. Vaginal examination revealed a small nulliparous uterus, but no definite abnormalities.

Laboratory Examination. The initial blood cell counts showed 3,250,000 erythrocytes; and 6200 leukocytes, of which 76 per cent were polymorphonuclear neutrophils, and 20 per cent lymphocytes. The blood Wassermann reaction was strongly positive. The resistance of the erythrocytes to hemolysis by hypotonic salt solution was greatly increased (hemolysis began at 0.34 per cent and was complete at 0.22 per cent). The blood platelets were diminished in number, the reticulocytes slightly increased, and the bleeding time and coagulation time normal. The presence of bilirubinemia was proved by a positive van den Bergh reaction. The urine was normal except for the presence of small amounts of bilirubin and bile salts, proving that the jaundice was obstructive.

Roentgenograms showed a destructive lesion and pathologic fracture of the left humerus (Fig. 1); a diffuse, sclerotic lesion, with periosteal proliferation, involving the left tibia, left fibula, and right tibia; destructive and sclerotic lesions, with periosteal proliferation, of both femora, especially the right; and a destructive process involving the right humerus. It was the roentgenologist's opinion that these lesions were syphilitic in nature.

Summary. History of anemia, intermittent slight jaundice, and splenomegaly, all of many years' duration, beginning early in life. History of sterility. Presence of mild obstructive jaundice, shrunken liver, splenomegaly, ascites, secondary anemia, leukopenia, diminished fragility of erythrocytes, widespread syphilitic lesions of the long bones, and a strongly positive blood Wassermann reaction; to these should be added slight melena and profuse epistaxis and hematemesis which supervened during patient's residence in the hospital.

Diagnosis. Tertiary syphilis (congenital?) of the liver and spleen, reproducing the clinical features of Banti's syndrome; syphilitic osteosclerosis, periostitis and caries of long bones; pathological fracture of the left humerus.

Subsequent Course. At first there was a slight remittent fever, never exceeding 101° F., which disappeared after ten days, not to return. The icterus was variable in degree, sometimes being absent entirely.

The steady accumulation of ascitic fluid necessitated three paracenteses (October 13, November 7, November 28, giving issue to 3000 cc., 3000 cc. and 5500 cc., respectively); the fluid was clear, greenish-yellow in color, of low specific gravity, contained from 8 to 13 gm. of albumin to the liter, contained no bile pigment or blood, and at first gave a strongly positive Wassermann reaction. The Wassermann on the fluid removed November 28, after the antisymphilitic treatment had begun to take effect, was only slightly positive.

The following antisymphilitic treatment was given: Potassium iodid by mouth, in daily doses of 1 gm.; potassium-bismuth-tartrate intramuscularly, in weekly doses of 0.1 or 0.2 gm., over a period of nine weeks (total 1.1 gm.); and, during the latter part of the period of bismuth administration, neoarsphenamin intravenously, in weekly doses of 0.2 or 0.3 gm. (total 1.4 gm.). The blood Wassermann reaction continued to be strongly positive after four weeks of treatment. The net result of this therapy was a 30 or 40 per cent reduction in the volume of the spleen, and complete healing

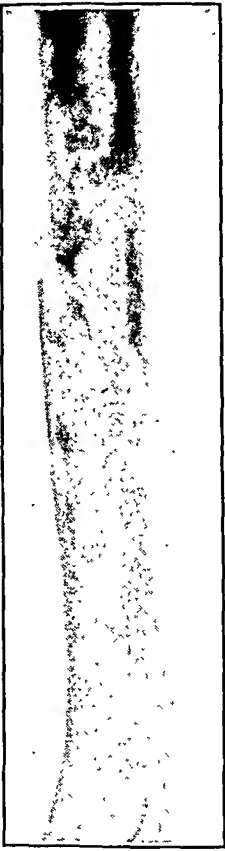


FIG. 1



FIG. 2



FIG. 3

FIG. 1.—Left humerus. Roentgenogram taken before starting antisyphilitic treatment, showing extensive syphilitic osteolysis and pathologic fracture. The fracture was a month old at this time, but there is no indication of a reparative process.

FIG. 2.—Left humerus. Roentgenogram taken during course of antisyphilitic treatment, showing beginning of callus formation about the pathologic fracture.

FIG. 3.—Left humerus. Roentgenogram of portion removed at autopsy, showing satisfactory bony union.



FIG. 4.—Left humerus. Photograph of portion removed at autopsy, showing complete healing of fracture.



FIG. 5.—Liver. Gross appearance of postmortem specimen, showing extreme deformity, and reduction in volume of right lobe.



FIG. 6.—Liver. Transverse sections, showing extensive scarring, especially about the hilus and throughout the shrunken right lobe.

of the pathological fracture (Figs. 2, 3, 4, and necropsy protocol); in other respects the patient's condition grew slowly but steadily worse.

Blood examination:

	Hb., per cent.	R.B.C.	W.B.C.
Oct. 3	45	3,110,000	6850
Oct. 30	50	2,380,000	
Dec. 4	54	2,460,000	4000
Dec. 19	30	1,800,000	4650

About December 1, 1928, there were brisk and repeated epistaxes; later the epistaxis was renewed, and hematemesis occurred. Transfusion of blood was resorted to several times with temporary benefit. Patient died of hematemesis December 20, 1928.

The question of whether or not splenectomy should be performed was considered seriously, but it was thought to be inadvisable without a preliminary course of antisyphilitic treatment, and later the patient's condition rendered it too hazardous. Judging from the state of the liver as discovered at autopsy, splenectomy would not have modified the course of the illness, except perhaps unfavorably.

Necropsy Protocol (Excerpts) (Dr. G. H. Hansmann). Skin very pale; skin and sclerae questionably icteric. Numerous petechiae and ecchymoses, especially over the lower extremities. Bloody discharge from the left nostril. Left humerus palpably thickened in its lower third, but no false motion at the site of thickening.

The left pleural cavity contained 350 cc. of bloody fluid; the right, 450 cc. of clear fluid. The inferior third of the right lung was covered as with a cap by thick, white, fibrous pleura which was extensively and firmly adherent to the chest wall, pericardium and diaphragm. The pleura at the base of the left lung was also thickened and adherent to the pericardium and diaphragm. The lungs showed no abnormalities of any consequence.

The heart and aorta showed no noteworthy changes.

The peritoneal cavity contained 1700 cc. of clear yellow fluid. The liver was removed only with the greatest difficulty because of the very dense, continuous adhesions between it and adjacent structures, particularly the diaphragm. As a whole, it presented the characteristic appearance of a *foie ficelé* (Figs. 5 and 6). Its weight was 950 gm. The right lobe was about one-fourth as large as normal, and one-third as large as the left lobe. It consisted of a group of irregularly shaped nodules measuring from $\frac{1}{2}$ to 5 cm. in diameter, separated by firm, deep scars; some of these lobules of liver tissue seemed almost normal. The consistency of this lobe was somewhat softer than that of the left; the cut surface presented a dark, mottled appearance. The left lobe presented a similar mottled appearance, and contained areas of bile-stained tissue which were thought to represent regenerated liver cells. Histologic examination showed many bands of dense fibrous tissue radiating from the capsule into the liver substance; much replacement of liver tissue by localized areas of scarring; some regeneration of liver cells in rounded lobules in which the normal architecture of the liver cords was disturbed; much stasis of bile; and no acute inflammatory lesions. The Levaditi stain failed to reveal any treponemata.

The gall bladder was thickened, and adherent to surrounding structures.

The spleen weighed 525 gm. Its capsule was thickened, and there was a pronounced perisplenitis, with firm adhesions to the liver and adjacent parietes. Its consistency was firmer than normal, and it cut with increased resistance. The cut surface showed chronic passive congestion, increase of connective tissue, and Malpighian corpuscles which were less than normally prominent. Histologically, thickening of the capsule and trabeculae, and rather marked atrophy of the parenchyma were observed—the latter

perhaps the result of the diffuse increase in supporting tissue. There were a few healed lesions containing calcium which were thought to represent old gummata.

The small intestine contained 355 cc. of clotted blood, and there was an area of capillary injection about 5 cm. in diameter situated in the posterior stomach wall near the cardia, but no varices were to be found in the lower esophagus or cardiac end of the stomach.

The kidneys were essentially normal.

The internal genitalia were not remarkable except that the uterus was unusually small. Histologically, the ovaries were normal and contained numbers of primordial ova.

The fractured humerus had healed completely by bony union (Figs. 3 and 4). Histologic examination of the bone showed irregularity of the cortex due to the presence of numerous bloodvessels leading from the periosteal to the medullary tissue; general thinning of the cortex and complete loss of its substance in areas of penetration by bloodvessels; thin, irregularly arranged trabeculae; perivascular infiltration and intimal thickening of the smaller bloodvessels; and a low-grade proliferative inflammation of the periosteum which had resulted in osteogenesis in the cortical tissue.

Summary. Healed lesions of syphilis, probably congenital, in the bones, liver and spleen. In the liver the extensive scarring had given rise to biliary and portal obstruction, producing jaundice, ascites, and hemorrhage from the intestinal mucosa.

Review of the Literature. A thoroughly exhaustive research of the literature of tertiary visceral syphilis reproducing the clinical features of Banti's syndrome would involve a greater amount of labor than is warranted by the nature of the subject. The present review is reasonably thorough and comprehends perhaps the most important cases, but it must not be supposed to exhaust the available material. The bibliography cites, in addition to the principal papers, a few references which were found to have appreciable collateral value.

In view of the facts that Banti's syndrome often requires many years for its evolution, during which time it passes through various stages which are none too well defined, that it is prone to exhibit little understood variations from the general course which it is supposed to pursue, and that its right to a position as a definite pathological entity has never been firmly established, it has not been deemed wise to erect too rigid a set of criteria for classification of cases. Nevertheless, some difference of opinion is likely to arise among students of the subject with reference to the classification attempted here. It has been found expedient to divide the cases into three groups. The first group comprises those cases of syphilis simulating Banti's syndrome which have been acceptably reported and are regarded as satisfactory for both categories beyond reasonable doubt (Table I). The second group includes cases which are for the most part highly suggestive of syphilis simulating Banti's syndrome, but are nevertheless open to serious question from one or another standpoint (Table II). The third group embraces cases which are held to be definitely excluded from the category (Table

III). Many of the cases cited in the third group are included not because of their intrinsic merit, but because they have been called into question by previous writers on the subject.

Satisfactory Cases (Table I). Except as indicated in the table, these cases are well authenticated, and do not require extended comment.

TABLE I.—SATISFACTORY CASES.

Date.	Author.	No. of cases.	Comment.
1900	Osler ^{57,58}	2	One autopsy; see text.
1901	Cayley and Wynter ¹³	1	Case report none too complete.
1902	Hocke ³⁹	1	Autopsy; the syphilis might be questioned.
1902	Chiari ¹⁵	2	Cases 1 and 4 of his paper; see text.
1904	Hochhaus ³⁸	1	Autopsy.
1905	Caussade and Milhit ¹²	1	Autopsy.
1911	Ridder ⁷⁰	1	
1911	Schmidt ⁷³	1	
1911	Weber ⁸³	1	Autopsy.
1912	Cattoretto ¹⁰	1	Second stage, Banti syndrome; syphilis possibly questionable.
1912	Neuberg ⁵⁶	1	
1913	Urrutia ⁷⁸	1	
1914	Anderson ²	1	
1914	Caussade and Levi-Frankel ¹¹	1	Autopsy.
1914	Hartwell ³⁵	1	Open to some question, especially the syphilis.
1914	Jeanselme and Schulmann ⁴⁰	1	
1914	Osler ^{59,60}	2	One autopsy; see text.
1914	Queyrat ⁶⁵	1	
1916	Giffen ³¹	3	
1916	Vance ⁸⁰	1	Autopsy.
1917	Resio ⁶⁷	1	
1918	Eason ²³	1	
1918	Resio ⁶⁸	1	
1919	Fawcett ²⁷	1	Syphilis possibly questionable.
1919	Resio ⁶⁹	1	Autopsy.
1924	Gonzalez Olachea ³³	1	
1925	Acuna and Maggi ¹	1	
1926	McCrae and Caven ⁴⁷	1	
1927	Bianchetti ⁷	1	
1927	Maniel and Nee ⁴⁵	1	Syphilis somewhat questionable.
1929	Korns	1	Autopsy; case reported herewith.

Total, 36

To Osler^{57,58} belongs the distinction of having recorded, in 1900, the first case of tertiary syphilis which reproduced the clinical features of Banti's syndrome. The autopsy report of the first case had been published in 1891 by Councilman.⁹³ In 1914, Osler^{59,60} amplified his descriptions of these cases, and added two more.

Chiari¹⁵ described 4 cases in all, but his Case III had already been recorded in detail by Hocke,³⁹ and the presentation of his second case is inadequate, particularly with reference to the anamnesis. His first and fourth cases are fairly satisfactory, although Leon-Kindberg⁴³ was inclined to look upon the evidence of syphilis as unconvincing. There were necropsies on all 4 cases.

Gonzalez Olachea³³ states that in 1923 he reported another case similar to the one referred to here.

Questionable Cases (Table II). *A priori*, one would not expect to find cases prior to the time of Banti's contributions which could be recognized clearly today as Banti's syndrome. This is indeed the fact, but there are nevertheless many highly suggestive cases, some of which barely miss meeting the essential requirements.

TABLE II.—QUESTIONABLE CASES.

Date.	Author.	No. of cases.	Comment.
1876	Goldstein ⁵²	1	His Case 2; autopsy; see text.
1879	Deakin ²²	1	His Case 1; autopsy; see text.
1886	Strümpell ⁷⁵	1	Autopsy; see text.
1895	Carslaw ⁹	1	Congenital syphilitic, aged eighteen years, with enlarged liver and spleen; no other details given.
1896	Coupland ¹⁹	1	Autopsy; see text.
1902	Musser ⁵⁴	1	Case of cerebrospinal syphilis with intercurrent jaundice, hepatic and splenic enlargement, gastrointestinal hemorrhages and moderate anemia.
1907	Thomas ⁷⁷	1	Possibly early stage of Banti's syndrome; see text.
1910	Hess ³⁷	3	His Cases 1, 5 and 6; inadequate case reports.
1910	Monaschkin ⁶⁰	1	Syphilis questionable; see text.
1910	Wagner ⁵²	1	Syphilis questionable.
1911	Fuhs ²⁹	1	Syphilis questionable.
1911	Vogel ⁸¹	1	Not clearly Banti's syndrome.
1912	Lindt ⁴⁴	1	Both Banti and syphilis open to question.
1912	Perussia ⁶⁴	1	Discussion in text.
1912	Vallardi ⁷⁹	1	Discussion in text.
1914	French and Turner ²⁹	1	Case report inadequate.
1915	Krull ⁴¹	2	His Case 2, syphilis, but not Banti's syndrome; his Case 3, evidence of syphilis only inferential; both cases autopsied.
1916	Clark ¹⁶	1	Both syphilis and Banti's syndrome questionable.
1919	Courtois-Suffit and Giroux ²⁰	4	Case reports incomplete.
1919	Symmers, Gettler and Johnson ⁷⁶	1	Their Case 4; see text.
1920	Miller ⁴⁹	1	Probably not syphilitic.
1924	Rohacek ⁷¹	1	Not clearly Banti's syndrome.
1925	Farley ²⁶	1	Not clearly Banti's syndrome.
1927	Curschmann ²¹	1	Description inadequate.

Total, 30

Goldstein's³² Case 2 had syphilis undoubtedly, and manifested some of the clinical features of Banti's syndrome, namely, icterus, enlargement of the liver and spleen, and late ascites. Necropsy showed that the liver was not much enlarged, and contained gummata; and that the spleen and lymph nodes were enlarged. His description, however, is so wanting in detail that one can do no more than classify the case as suggestive.

Deakin's²² Case 1 is even more suggestive than Goldstein's, but

his description is also inadequate, particularly with respect to the history. The patient had anemia, ascites, slight icterus, and enlargement of the liver and spleen. Death was caused by hematemesis. Necropsy showed that the left lobe of the liver was nearly equal in size to the right, and that the organ contained many gummata, one of which was obstructing the portal vein. Glisson's capsule was thickened and firmly adherent to the stomach and diaphragm, and there was a proportionate degree of perisplenitis. The spleen weighed 680 gm. No varices were found in the gastrointestinal tract.

Strümpell's⁷⁵ case, as Peiser⁶³ reports it, is also inadequately described. The patient, who was aged fifty years, was said to have had splenomegaly twenty-two years earlier. He had been ill for two years with fever and pain. He had an enlarged liver and spleen, and while under observation developed ascites and slight icterus. Necropsy revealed syphilis of the liver, chronic perihepatitis and perisplenitis, and splenomegaly.

Coupland's¹⁹ case is of especial interest because it has been referred to by so many writers, but his description, which is extremely brief, by no means fulfills even the most elementary requirements of Banti's syndrome. It was simply a patient with enlarged spleen and anemia who improved greatly after splenectomy, but died two years later from hematemesis. The necropsy disclosed a typically scarred liver and varices of the rectum and esophagus.

Thomas's⁷⁷ patient gave a history of a chancre, and of weakness and epistaxis. He was pale, and his liver was greatly enlarged, filling the entire right upper quadrant of the abdomen; the spleen extended 16 cm. below the costal margin. Antisymphilitic treatment effected great reduction of the hepatic enlargement, slight reduction of the splenic enlargement, and pronounced improvement of the patient's general condition. Except for the excessive amount of hepatic enlargement, this case may be thought to reproduce an early stage of Banti's syndrome fairly acceptably, but the case report is deficient in respect to several essential details.

Monaschkin's⁵⁰ case presented many of the clinical features of Banti's syndrome, but, as he himself indicates, the evidence of syphilis is incomplete. However, two of his reasons for excluding syphilis, namely, that antisymphilitic treatment was ineffectual, and that the blood changes were not characteristic, especially because there was leukopenia rather than leukocytosis, are invalid, as the accumulated experience with cases of this kind has demonstrated conclusively. The Wassermann reaction was positive, but as an isolated observation this cannot be regarded as proof of syphilis.

The cases reported by Perussia⁶⁴ and Vallardi⁷⁹ are as baffling as they are interesting. Both were diagnosed "anemia splenica," but in neither was there anything in the history, physical examination, or serological tests, to suggest syphilis. Notwithstanding this fact, both patients were vastly improved by intravenous injections of

salvarsan. Vallardi's patient had had malaria two years before, but no plasmodia were demonstrable while he was under observation. Vallardi regarded syphilis as definitely excluded in his own case; Perussia contented himself with speculation. Both cases defy exact classification.

Symmers, Gettler and Johnson⁷⁶ present 6 cases, but only one of them (their Case 4) is described in sufficient detail to warrant consideration. Certain features of this case incline one to include it among the number of cases regarded as proved, but unfortunately the published report is wanting in several important respects.

Cases Not Included (Table III). Of the cases cited by Barthelemy,⁵ only that of Gouraud is worthy of notice, but the question of what part the known malaria played in the etiology cannot be answered. The patient was a girl, aged thirteen years, who had suffered gradual enlargement of the abdomen; the spleen was enormous, the liver small. Icterus appeared during the last month of life. Death occurred from rupture of a circum-umbilical varix. At autopsy, the liver was found to be small (880 gm.), and was umbilicated and cut through by thick fibrous bands. The spleen measured 22 by 12 cm. and had a thickened capsule.

TABLE III.—CASES NOT INCLUDED.

Date.	Author.	No. of cases.	Comment.
1870	Moxon ⁵²	1	Autopsy; not Banti's syndrome.
1876	Goldstein ³²	1	His Case 1; autopsy; no splenomegaly.
1877	Bramwell ⁸	1	Inadequately described.
1883	Engel ²⁵	1	Syphilitic hepatitis, not Banti's syndrome.
1884	(Barthelemy) ⁵		
	Barth	1	Not Banti's syndrome.
	Berne	1	Not Banti's syndrome.
	Crequy	1	Not Banti's syndrome.
	Dittrich	2	Both autopsied; not Banti's syndrome.
	Dowse	3	Not Banti's syndrome.
	Gouraud (1863)	1	Autopsy; see text.
	Tissier	1	Not Banti's syndrome.
1886	Bartels ⁴	1	Case report inadequate.
1886	Fournier ²⁸	1	Case report inadequate.
1886	(Peiser) ⁶¹		
	Frerichs (1861)	4	Three autopsies
	Hjelt (1861)	1	Autopsy
	Chvostek (1863)	1	
	Vecchi (1869)	1	
	Goodbridge (1871)	1	Autopsy.
	Riegel (1872)	1	Autopsy
	Picot (1872)	1	Autopsy
	Key (1873)	1	Autopsy
	Loewenfeld (1873)	2	Both autopsied
	Lacombe (1873)	1	Autopsy
	Martineau (1875)	1	Autopsy
	Dusaussay (1876)	1	
	Key (1878)	1	Autopsy
	Chvostek (1881)	11	Eight autopsies
	Kahl	2	Both autopsied
	Schützenberger	1	

Discussion in text.

Date.	Author.	No. of cases.	Comment.
1891	Chauffard ¹⁴	1	A congenitally syphilitic baby with enlarged liver and spleen; not Banti's syndrome.
1894	Otto ⁶¹	7	Secondary syphilis with icterus; see text.
1897	Cole ¹⁷	2	Spleen not mentioned.
1897	Schlichthorst ⁷²	1	Marchand's ⁴⁶ Case 1; autopsy; syphilis not proved.
1900	Guerin ³⁴	1	Not Banti's syndrome.
1900	Menetrier ⁴⁸	1	Autopsy; hypertrophic cirrhosis; see text.
1900	Peabody ⁶²	1	Not Banti's syndrome.
1901	Einhorn ²⁴	10	Not Banti's syndrome.
1902	Stockton ⁷⁴	3	No splenomegaly.
1902	Weinberger ⁸⁵	1	No evidence of syphilis.
1903	Marchand ⁴⁶	2	One autopsy; see text.
1904	Bernard ⁶	1	Simulated hypertrophic biliary cirrhosis.
1905	Aspelin ³	4	Banti's syndrome, but not syphilis.
1908	Naegeli ⁵⁵	1	Case not adequately reported.
1910	Hayn and Schmitt ³⁶	1	Laboratory statistics; no clinical report.
1910	Hess ³⁷	3	His Cases 2, 3 and 4; syphilis questionable and case reports inadequate.
1911	Moore ⁵¹	1	Autopsy; no evidence of syphilis.
1912	Mullally ⁵³	1	Autopsy; not Banti's syndrome.
1913	Core ¹⁸	1	Case report inadequate.
1914	Lemaire ⁴²	1	Acquired hemolytic icterus; not Banti's syndrome.
1914	Leon-Kindberg ⁴³	1	No evidence of syphilis.
1919	Symmers, Gettler and Johnson ⁷⁶	5	Their Cases 1, 2, 3, 5 and 6, all inadequately described.
1919	Weil ⁸⁴	5	His Cases 6, 7, 8, 11 and 12; descriptions meager; syphilis not proved.
1926	Raynaud, Nanta and Lacroix ⁶⁶	2	Banti's syndrome, but not syphilis.
		Total,	104

With the exception of Strümpell's and Deakin's cases, both of which have been discussed under Table II, it is impossible to construe as Banti's syndrome any of the numerous cases catalogued by Peiser.⁶³ It is perhaps correct to say that all were cases of syphilis of the liver, but it would be unprofitable to attempt further classification.

Syphilitic icterus is Otto's⁶¹ thesis. He refers at some length to the cases of Vecchi, von Jastrowitz, Picot, von Schleuthauer, Beck, and Roth and Tommasi, which obviously do not fall within the category of Banti's syndrome, and reports 7 cases of secondary syphilis, all with icterus, none of which simulated Banti's syndrome.

The case recorded by Menetrier⁴⁸ might have been mistaken for Banti's syndrome had it not been for the enormously enlarged liver (2800 gm.), which was the seat of a hypertrophic cirrhosis, and was studded with gummata. The spleen weighed 1750 gm. The patient was a woman, aged forty-six years, a chronic alcoholic. Her illness

of three years' duration was characterized by painless swelling of the abdomen, epistaxis, and secondary anemia; toward the end ascites developed, but never icterus.

Marchand's paper⁴⁶ demands particular attention because of the fact that it has been referred to by so many writers on the subject of syphilis and Banti's syndrome. In his first case, which was really Schlichthorst's, there was no satisfactory proof of syphilis. His second case was that of a boy whose illness extended from his thirteenth to his sixteenth years, when he died of secondary anemia from repeated hematemesis. He had chronic splenomegaly, ascites, leukopenia, secondary anemia, and slight enlargement of the liver, but no icterus. At necropsy the spleen weighed 830 gm. and the liver 1390 gm. The latter showed cirrhosis and granular atrophy. No mention of gummata was made. That this was clinically a fairly good case of Banti's syndrome cannot be questioned seriously, but Marchand's contention that congenital syphilis played an etiologic rôle was based purely upon rather precarious anatomic grounds, and is unconvincing. His third case is invalidated by a history of malaria and the presence of widespread tuberculosis of the lungs and intestines, as well as by the fact that the evidence of syphilis was merely hypothetical. It was presumably to this case that Schmidt⁷³ referred when he said that one of Marchand's cases proved later to be kala-azar, for Marchand's first and second cases were controlled by autopsy. There is no justification, therefore, for including any of Marchand's cases in the category of Banti's syndrome reproduced by syphilis.

Discussion. One carries away from a study of the literature of this subject a number of rather definite impressions. Rolleston's¹¹⁹ observations with reference to the character of the pathologic alterations in the liver can be appreciated at their true value. Of the polymorphic lesions which he describes the sclerogummatous form occurs most frequently. The liver is reduced in size (weights as low as 700 gm. have been recorded) and is so "widely fissured and lobulated" by linear and stellate cicatrices, the residua of healed gummata, "that the shape of the liver may be altered out of all recognition." In this state it has been aptly termed *foie ficelé* by the French writers. "The relative size of the two chief lobes of the liver may be greatly altered; thus, the left lobe may be almost entirely destroyed by fibrous contraction, or enlarged from gummatous infiltration or from hyperplasia of the liver substance to compensate for extreme destruction of the right lobe." Rolleston attributes the splenomegaly to amyloidosis or gummatous infiltration, but in the necropsy protocols of cases simulating Banti's syndrome which I have examined, it appears that a relatively simple interstitial fibrosis is the usual cause. Rolleston refers to Cheadle's statement that syphilis is the most important cause of perihepatitis, but his own experience is that "gummas commonly

cause local perihepatitis, but that syphilitic infection is quite an exceptional cause of universal perihepatitis." In the group of cases here reviewed the evidence favors Cheadle's opinion. Thickening not only of Glisson's capsule, but also of the capsule of the spleen, with dense and extensive synechiæ to the diaphragm and adjacent viscera is of almost universal occurrence. In Vance's⁸⁰ case the left half of the diaphragm was said to be $3\frac{1}{2}$ inches thick! In my own case the liver was completely hidden in a nest of dense scar tissue, of which the diaphragm formed an integral part. Surgeons undertaking splenectomy almost invariably experience great difficulty in freeing the spleen from its numerous adventitious attachments. Further discussion relating to pathology may be found in the papers of Chauffard,¹⁴ Grenier,¹⁰⁰ and Moschcowitz.¹¹⁰

The secondary anemia, leukopenia, and relative lymphocytosis characteristic of Banti's syndrome are found likewise in tertiary hepatic syphilis which reproduces that syndrome. Intermittent jaundice, usually mild, and generally obstructive in type; recurrent ascites; hemorrhage, either from the nose or stomach; and pain in the upper quarters of the abdomen, are of frequent occurrence. Schrager¹²⁰ and Rolleston,¹¹⁹ among others, have emphasized the importance of pain as a symptom of syphilitic hepatitis. The general semeiology has been discussed at length by Gerhardt,⁹⁸ Peiser,⁶³ Otto,⁶¹ Weber,⁸³ Vance,⁸⁰ and others.

The diagnostic criteria of Banti's syndrome need not be recited, nor should it be necessary to insist upon the institution of anti-syphilitic treatment in cases of Banti's syndrome in which syphilis is known or can be proved, but it is necessary to insist with all possible emphasis upon a thorough trial of antisypilitic treatment in every case of Banti's syndrome before syphilis is finally excluded. No other single fact emerges so imperatively from the literature of this subject. Time and time again the fundamental rôle of syphilis has been overlooked because it was not suggested by the history, by unequivocal physical signs, or by serologic tests, and was only discovered at operation or autopsy. The well-known fact that in the late stages of the syndrome, when most of the liver has been replaced by scar tissue, antisypilitic treatment may be largely or wholly ineffectual, in no wise constitutes an exception to the rule demanding a therapeutic test.

In the treatment, potassium iodid, bismuth and mercury should be given first consideration. The most conspicuous therapeutic successes with mercury and potassium iodid, separately or in combination, are those which have been reported by Guerin,³⁴ Chauffard,¹⁴ Thomas,⁷⁷ Anderson,² Clark,¹⁶ and McCrae and Caven.⁴⁷ Syphilologists of today would perhaps frown upon the use of arsenicals, yet a great many of these cases have been treated energetically and successfully with one or another of the arsphenamins, for example, Perussia,⁶⁴ Vallardi,⁷⁹ Schmidt,⁷³ Curschmann,²¹ Urrutia,⁷⁵

Cattoretti,¹⁰ Jeanselme and Schulmann.⁴⁰ Two years after Schmidt's report, Curschmann⁹⁴ stated that the patient continued to enjoy excellent health. In the earlier stages of the disease, when great benefit is to be expected from antisyphilitic treatment, splenectomy is rarely indicated, but this is not necessarily true in the later stages, even if the medicinal treatment continues to be to a certain extent efficacious. Coupland's¹⁹ experience first called attention to the fact, subsequently emphasized by Giffen³¹ and others, that under certain circumstances splenectomy is an essential part of the treatment.

Summary. A case of tertiary syphilis of the liver which manifested itself as Banti's syndrome in the terminal stages is reported.

The literature of tertiary syphilis of the liver reproducing the clinical features of Banti's syndrome is reviewed, from which 36 approved cases, and 30 questionable cases, are collected. One hundred four additional cases, many of which have been cited frequently in the literature, are excluded from the category.

The pathology, semeiology and treatment are discussed briefly. In particular, the great importance of applying the therapeutic test to every case of Banti's syndrome before excluding syphilis as a possible etiologic factor is reëmphasized.

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AN EXPERIMENTAL STUDY OF THE REACTION OF THE CONTENTS OF THE TERMINAL PORTION OF THE ILEUM.*

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AMONG the factors which influence the reaction of the contents of the gastrointestinal tract may be mentioned saliva, food, gastric secretion, bile, pancreatic juice, intestinal secretions, bacterial putrefaction and the cleavage products of digestion. Statements to the effect that one type of food increases acidity and another decreases acidity are common, but there are few experimental data to show that the reaction of the contents of the intestinal tract can be appreciably changed by variations in the normal diet. It was thought that a study of the hydrogen-ion concentration of the intestinal contents, at frequent intervals throughout the process of digestion of various kinds of food, might throw some light on the subject.

A number of the questions which suggest themselves are: (1) What is the hydrogen-ion concentration of the contents of the terminal portion of the ileum of a dog fed a well-balanced diet at various periods during the process of digestion? (2) What changes in the hydrogen-ion concentration occur when the protein-fat-carbohydrate ratios are varied? (3) What, if any, relationship is there between the hydrogen-ion concentration and the time after the intake of food?

Literature. McClendon, Bissel, Lowe and Meyer (1920) after a thorough review of the literature on this subject concluded that there is lack of agreement in regard to the reaction of the intestinal contents and the changes brought about by various diets. Since then, however, other significant facts have been reported.

Okada and Arai (1922) found the reaction of the contents of the ileum of dogs to vary between hydrogen-ion concentration 6.59 and 7.83; readings were taken one, two and three hours after the dogs had been fed a pound of meat.

Abrahamson and Miller (1925) fed adult male albino rats different diets, some consisting largely of carbohydrates, some mainly of protein and others mainly of fat. They observed an average variation in the hydrogen-ion concentration of only 0.1 to 0.2 in the stomach and small intestine. Their readings uniformly showed acid in the lower half of the small intestine. The animals were killed several hours after their last meal and the hydrogen-ion concentration of the contents was determined colorimetrically.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

Redman, Willimott and Wokes (1927) found the average hydrogen-ion concentration of the contents of the ileum of guinea pigs to be pH 7.4, while that of normal adult rats was 6.8 and of young rats (one to three months old) 7. High-fat and low-fat types of rachitogenic diets when fed to rats induced greater acidity throughout the intestinal tract if vitamin D was added, but in the absence of vitamin D the fecal reaction became alkaline. They could not produce marked alteration in the intestinal hydrogen-ion concentration by varying the protein-fat-carbohydrate ratios of normal diets. It was found that the acidity of the contents of the stomach and duodenum tends to increase during the first four hours after the ingestion of a meal. In the remainder of the tract, however, an appreciable difference could not be observed in the hydrogen-ion concentration obtained when the time between feeding and death was between one and a half and four and a half hours. Only when food was withheld for as long as seventeen hours was the acidity much greater throughout the small intestine. A hydrogen electrode was used for making the determinations. Yoder (1927), working with the quinhydrone electrode, obtained similar results. He did not present readings for animals on normal diets.

Grayzel and Miller (1928) summarized their work on dogs as follows: "The reaction of the intestinal contents of dogs fed on a normal mixed diet is acid practically throughout the entire length of the tract, the cecum and colon showing somewhat less constancy in the results than the other levels of the tract. The hydrogen-ion concentration of the small intestine varies between 5.7 and 6.6. The reaction of the intestinal contents of dogs fed high-fat, protein, or carbohydrate diets is practically within the normal range of each level of the tract." The dogs were killed by intravenous injections of amytal four to six hours after their last meal. The abdominal cavity was then opened and the small intestine divided into sections, 60 cm. in length. The reaction of the contents of each section was then determined. It was shown that dilution did not appreciably affect the hydrogen-ion concentration and that the readings by the colorimetric and electrometric methods agreed closely. The colorimetric readings were on the average about pH 0.2 lower than those obtained by the electrometric methods.

While working on intestinal absorption, Hosoi, Alvarez and Mann (1928) observed that the intestinal contents of dogs were neutral except on one occasion when hashed meat was fed; the contents then had a slightly alkaline reaction. They used dogs in which the colon had been removed and the ileum anastomosed to the rectum. The reaction of the contents thus obtained was determined with litmus paper. Childrey, during the study of a similar problem, found the contents of the small intestine of dogs to be alkaline to litmus in the majority of instances.

Method of Procedure. Three apparently healthy dogs were chosen for study. They were prepared by an operation devised by Bollman and Mann so that the contents of the ileum could be readily obtained at frequent intervals. Two of the dogs had fistulas formed by resecting a section of ileum about 5 cm. long and about 15 cm. from the ileocecal juncture. The blood supply to the resected portion was maintained, the continuity of the tract completed by means of an end-to-end anastomosis, and the fistula formed by means of an end-to-side anastomosis between the resected portion and the ileum immediately below the site of the end-to-end anastomosis. The important step in the operation is to turn the resected section of bowel so that the peristaltic impulses pass, from without, in toward the ileum. Thus little, if any, intestinal content passes out onto the skin and the wound will usually heal by first intention and the dogs can be kept in good condition.

The third dog was prepared by a method which required a two-stage operation: removal of the colon and an end-to-end anastomosis between the terminal portion of the ileum and the rectum and removing the rectum and joining the ileum to the anus. The end result of this operation was just as satisfactory as that of the other operation but it required more time and was technically more difficult. Before selecting the operations described several other operations were tried and found to be impractical or unsatisfactory.

Determinations of hydrogen-ion concentration were not made until at least two weeks after operation at which time the dogs were apparently normal.

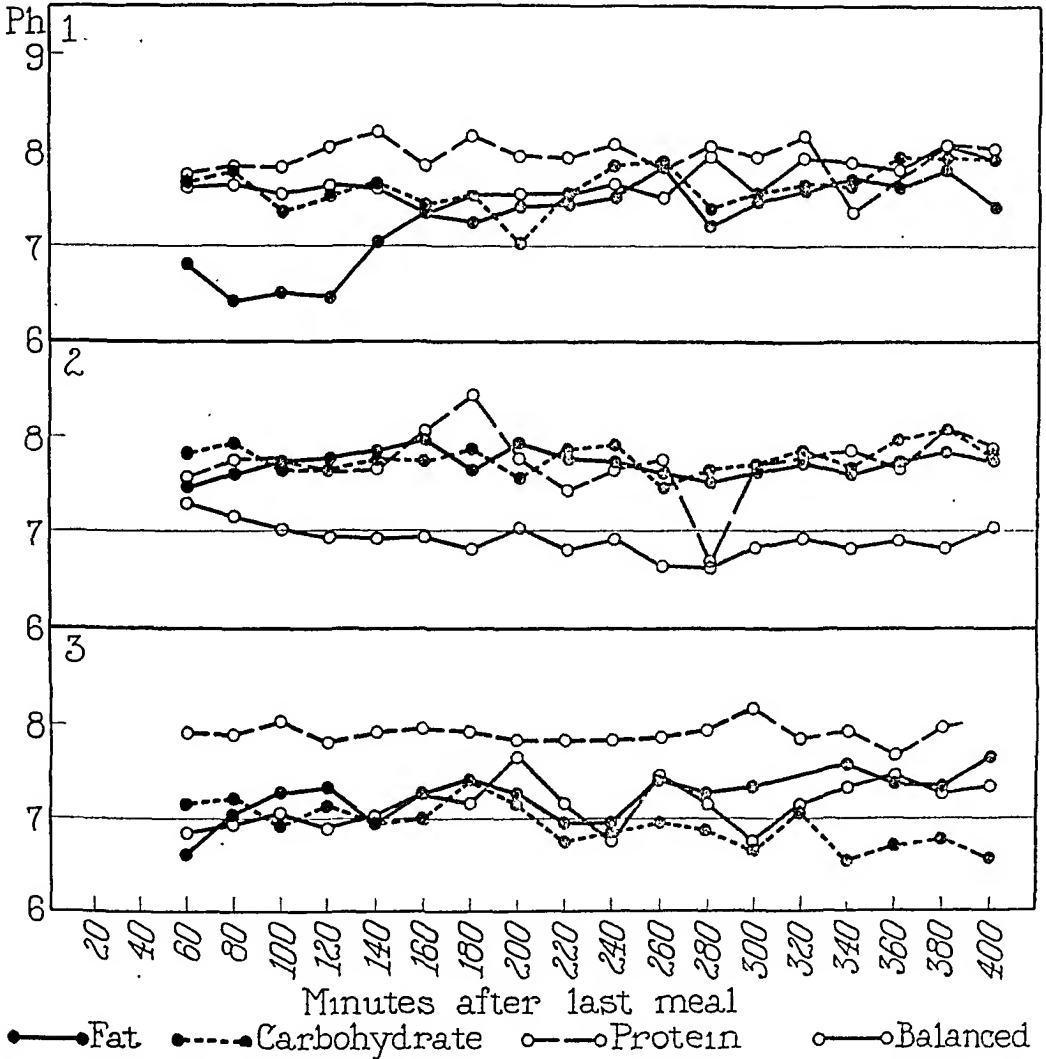
The diets chosen were: (1) High-fat in the form of fat horse meat; (2) high-protein in the form of lean horse meat; (3) high-carbohydrate in the form of cracker crumbs, skimmed milk and Karo syrup in proper proportions to make a thin paste; (4) whole milk. In each instance the dog was fed a given diet for two days and determinations of hydrogen-ion concentration were made on the third day. On the days that examinations were to be made the dogs were fed as much as they would eat in twenty minutes.

Determinations of hydrogen-ion concentration were made every twenty minutes beginning one hour after the last meal and continuing as long as sufficient material could be obtained, usually about seven hours. The contents were obtained by inserting a small rubber tube into the ileum and either aspirating or allowing the material to flow out, depending on its consistence. Whenever necessary a little distilled water was injected to aid in the collection of the material.

The hydrogen-ion concentration was determined with the aid of the quinhydrone electrode introduced by Biilmann (1921) and by a Leeds and Northrup potentiometer. Robinson (1925) compared the results obtained with the hydrogen and quinhydrone electrodes on a series of specimens of feces whose hydrogen-ion concentration

ranged from pH 5 to 7.8 and found the difference to be 0 to 0.3 with an average of less than 0.1.

After one set of observations had been completed the process was repeated and an average of the two used to chart a curve of the hydrogen-ion concentration at different intervals after a meal. More than 400 determinations were made.



The hydrogen-ion concentration of contents of the ileum of three dogs.

Results. After a high-fat meal the contents obtained from the ileum were yellow and of a semifluid consistence. The hydrogen-ion concentration varied between pH 5.7 and 8.15 with an average of 7.42.

After a high-protein meal a dark-brown homogeneous fluid was obtained. The hydrogen-ion concentration varied between pH 7.18 and 8.49 with an average of 7.86. These results were the most constant obtained.

The hydrogen-ion concentration of the ileal content, following a high-carbohydrate diet, was less constant than after a high-protein meal. It varied between pH 6.22 and 8.37 with an average of 7.42,

which was the same as the average following a high-fat diet. The material obtained was semifluid, containing yellow flakes.

After a diet of whole milk the ileal contents were fluid with bright yellow flakes similar to that noticed after a carbohydrate meal. The hydrogen-ion concentration varied between pH 6.33 and 8.08, with an average of 7.86, which was the same as the average hydrogen-ion concentration following a high-protein diet.

The tabulation shows the maximal, minimal and average hydrogen-ion concentration for each dog and each diet. The three graphs herewith were plotted from the average of the two sets of readings that were taken on each dog.

Comment and Conclusions. The results of this study cannot be said to be either in agreement or in disagreement with those of any previous investigators because the methods followed have been entirely different from those used by others.

After a diet of horse fat the contents obtained from the ileum of the first dog had a hydrogen-ion concentration ranging from the acid to the alkaline side of 7. When the readings were repeated, however, the contents were all alkaline. The contents obtained from the ileum of the second dog were all alkaline whereas those from the third dog were both acid and alkaline each time. The excursions of the hydrogen-ion concentration on the acid side were greater after a diet of fat than after any of the other diets, although the average of all readings was the same as when carbohydrates were fed. Such observations are not in agreement with those of Grayzel and Miller, and McClendon and his coworkers who found the reaction of the intestinal contents of the dog to be acid at all times.

After a high-protein diet the reaction of the ileal contents of all three dogs were alkaline at all times. This, however, is not in agreement with the results of Okada and Arai, McClendon and his collaborators and Grayzel and Miller, who found the intestinal contents to have an acid reaction.

After a high-carbohydrate diet the reactions of the ileal contents in the first dog were both acid and alkaline, of the second dog always alkaline, and of the third dog always alkaline. For the second dog all the readings showed acid the first day but when the study was repeated, both acid and alkaline results were obtained. Acid and alkaline results were also obtained when the third dog was studied.

Several possible sources of variation in readings should be mentioned: (1) The exposed intestinal tract is open to infection; (2) irritation caused by inserting a tube into the ileum frequently may give rise to variations in the amount of intestinal secretion; (3) in the early and late periods of observation only a scant amount of content is obtainable. There is no evidence, however, that these possible variations vitiated the results appreciably.

These data are presented without explanation, for to explain them would require a comprehensive study of the chemistry and probably

the bacteriology of the gastrointestinal tract and also a detailed study of the reactions of other portions of the tract from the stomach to the rectum.

Summary. Observations were limited to the contents of the terminal portion of the ileum of the dog. The dogs were prepared so that the contents could be obtained at frequent intervals. Thus a large number of determinations could be made on a few dogs. The influence of anesthesia or death was eliminated.

When the dogs were fed a high-fat diet the hydrogen-ion concentration of the ileal contents varied between pH 5.71 and 8.15 with an average of 7.42. After a high-protein diet the hydrogen-ion concentration varied between pH 7.18 and 8.49 with an average of 7.86. After a high-carbohydrate diet the hydrogen-ion concentration varied between pH 6.22 and 8.37 with an average pH 7.42. After a balanced diet the hydrogen-ion concentration varied between pH 6.33 and 8.08, with an average of 7.86.

HYDROGEN-ION CONCENTRATION OF ILEAL CONTENTS OF THREE DOGS ON VARIOUS DIETS.

	High-fat diet.			High-protein diet.			High-carbohydrate diet.			Balanced diet.		
	Max- imal, pH.	Min- imal, pH.	Aver- age, pH.	Max- imal, pH.	Min- imal, pH.	Aver- age, pH.	Max- imal, pH.	Min- imal, pH.	Aver- age, pH.	Max- imal, pH.	Min- imal, pH.	Aver- age, pH.
First dog	8.01	5.71	7.27	8.49	7.37	7.95	7.15	6.89	7.63	8.08	7.25	7.67
Second dog	8.15	7.35	7.71	8.45	7.18	7.73	8.37	7.22	7.76	8.00	6.33	6.96
Third dog	7.67	5.81	7.30	8.18	7.67	7.90	7.43	6.22	6.87	7.83	6.59	7.27
Average	7.42	7.86	7.42	7.86

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FATAL EMETIN POISONING, DUE TO CUMULATIVE ACTION, IN AMOEBIC DYSENTERY.

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IN view of the increasing prevalence of amœbiasis throughout the United States, as has been pointed out by Kofoed,¹ Dowling,² Smithies,³ and others, it is desirable to realize the importance of this disease, no longer tropical, and the occasional accidents in its treatment. The Gulf and Pacific Coast States, still lead with the greatest number of infections, but it is surprising to note the great number of carriers found in Philadelphia by deRivas and Fife⁴ and in Chicago by Smithies.³

It is a regrettable fact that so little is known about the chemistry and pharmacology of emetin, and its action on the *Entamoeba histolytica*. It is not the purpose of this paper to add new experimental data to our knowledge of this drug, but to point out the discrepancies and confusions of opinion that occur in the literature regarding the action, dosage and toxicity of emetin. I also wish to show that poisoning, which may be fatal, may and does occur even in doses much smaller than the heretofore considered minimal lethal dose.

Summary of Case Record. The patient was a female, aged twenty-one years, a university student. In the latter part of August, 1928, she spent a few days in the mountains and drank water from a glacial stream. On returning to Seattle early in September, she began to have our or five watery stools a day, accompanied by cramp-like pains in the epigastrium, and by a respiratory embarrassment which would cause her to sit up to breathe. She began to lose weight slowly, but this was attributed to her loss of appetite and decreased food intake. The physical examination was completely negative, except for a slight tenderness over the course of the colon. The body weight was about 100 pounds.

She entered the hospital on January 2, 1929, for diagnosis and treatment. The laboratory reported a hemoglobin of 82 per cent; white blood count, 8600 cells per c.mm.; a differential count of 70 polymorphonuclear leukocytes and 30 lymphocytes. The Wassermann reaction was negative. The urine showed a faint trace of albumin. *Entamoeba histolytica* was found in the stool.

The following treatment was instituted: The large bowel was irrigated twice daily with a 1 to 3000 solution of quinin bisulphate, and emetin hydrochlorid, 0.02 gm., given intravenously morning and night for ten days (20 injections). After this time no amœba were found in the stool. There was no nausea, vomiting or other gastrointestinal symptoms at any time. The bowels moved two or three times daily without pain, the stools being soft, but well formed. The tenderness in the abdomen had disappeared. After a rest period of one week, during which time one quinin irrigation was given daily, the emetin was resumed and given for four days only (8 inec-

tions). On January 23 the patient left the hospital with amœba-free stools after repeated examinations since January 15.

Shortly after returning home amœbæ were again found and the diarrhea and tenderness returned. She also noted that she tired easily, and had some vague pain in the legs when walking to and from her classes about the campus. On February 2 she was readmitted to the hospital. The following treatment was ordered, modified after that of Bethea.⁵

First Period. Five days: 0.065 gm. of emetin hydrochlorid injected daily into the deltoid muscles. No other medication during this period. Full typhoid diet up to 3000 calories daily.

Second Period. Ten days: Emetin continued as above; 2.3 gm. of ipecac given daily in enteric coated pills. These pills were freshly prepared. During this second period the patient was given a daily colonic irrigation of 2 gm. of quinin sulphate in $\frac{1}{2}$ gallon of warm water. The typhoid diet was continued, but while the ipecac pills were being given at bedtime, the patient received soft diet during the day up to 1 P.M., after which time she received nothing but simple liquids, as water, tea, black coffee, bouillon or ginger ale.

The treatment for the first period was carried out, and the first three days of the second period, when treatment was discontinued due to vomiting.

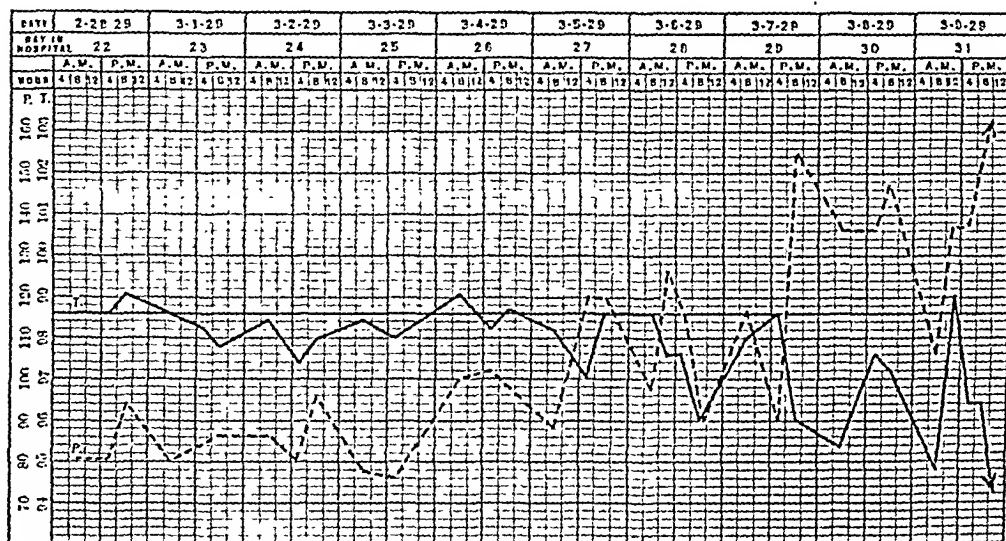
MEDICATION GIVEN WITH RESULTS NOTED.

Date.	Drugs given.	Amount given, gm.	Results noted.	Laboratory report.	Remarks.
Feb. 8	Emetin	0.065			
Feb. 9	Emetin	0.065			
Feb. 10	Emetin	0.065			
Feb. 11	Emetin	0.065			
Feb. 12	Emetin	0.065	Nausea	Amœbæ present.	
Feb. 13	Emesis	Medication discontinued.
Feb. 16	Ipecac	2.300	Emesis in 3 hrs.		
Feb. 17	Emetin	0.065	Emesis		
	Ipecac	2.300	Emesis		
Feb. 18	Emetin	0.065	Emesis	Amœbæ present	Medication discontinued.
	Ipecac	2.300	Emesis		
Feb. 21	Emetin	0.065	Emesis	Medication discontinued.
	Ipecac	2.300	Emesis		
Feb. 25	Emetin	0.020*	Nausea	Amœbæ present; few pus cells; blood 1+	
Feb. 26	Emetin	0.020*	Appetite poor; no nausea	Medication discontinued.
Feb. 28	Emetin	0.020*	Appetite poor; restless	Medication discontinued.
Mar. 2	Emetin	0.020*	Appetite poor; restless		
Mar. 3	Emetin	0.020*	Appetite poor; restless	Amœbæ present; few pus cells	Medication discontinued sedatives ordered.
Mar. 7	Amœbæ present; blood 2+	

* Twice daily.

The chronologic data in table shows the amount of medication given daily and the results noted.

On March 3, after spending several restless nights, the patient asked for a rest period, as she was feeling weaker. The pulse was good, averaged 80 to 85; the temperature and respiratory rate were normal. Sedatives were given in small amounts, with poor results. On March 4 the pulse rose to 100; on March 5, to 120 and the temperature fell to 97° F. She was weaker, more restless and developed symptoms of a mild peripheral neuritis. From this date the temperature continued to fall, associated with a corresponding increase in the pulse and respiratory rate. (See graphic chart.) On March 7 a consultation was held. There was evidence of a mild myocarditis and digalen was given every four hours. The prognosis was very good. On the morning of March 9 the respirations became rapid, the pulse very weak, and the patient became cyanotic; 500 cc. of 5 per cent glucose in physiologically normal saline were given intravenously, with 12 units of insulin. She promptly felt relieved and the symptoms disappeared. The consultant again pronounced the heart to be in good condition and made a very favorable prognosis. That evening the symptoms returned, but were less severe. An intravenous injection of saline and glucose was started and after 200 cc. were given she showed no improvement. Gradually the respira-



tions became very embarrassed, cyanosis deepened and the pulse could not be felt. At this turn in her condition adrenalin, in 1 to 10,000 solution, and caffein sodium benzoate were given slowly intravenously (1 cc. in two minutes), being injected with the glucose, without response. She expired in a few minutes.

AUTOPSY. At autopsy little was found except at the point of entrance of the ileum into the cecum, where there were several scars, as from healed ulcers. Just lateral to the opening of the ileum there was a small ulcer 0.66 cm. in diameter. The entire large intestine was examined for ulcers. No other ulcers were found. There were several scars as from healed ulcers. The arterial supply to the intestinal tract was normal. The veins were dilated throughout to about one and a half to two times normal size. The heart grossly showed a slight myocarditis. The microscopic examination of the tissues showed a marked parenchymatous degeneration of the liver, most marked about the central veins. There was an acute diffuse nephritis and an acute parenchymatous degeneration of the adrenals. The spleen showed an acute hyperplasia due to toxemia. Death was apparently due to a condition of shock, probably produced by the cumulative action of some toxic substance.

Summary of Case. A young female, weighing about 100 pounds (37 kg.) received 0.56 gm. of emetin hydrochlorid from January 2 to January 23: During the second admission to the hospital she received 0.72 gm. of emetin, from February 2 to March 3. The total amount of the drug received, over a period of about two months, was 1.28 gm., or 0.034 gm. per kg. of body weight. After the first series of treatments the disease appeared to be cured. There was a relapse, and she returned to the hospital for further treatment. This was carried out with but moderate success, when the emetin was discontinued, due to general debility of the patient. Six days after the drug was discontinued, death occurred from a vasomotor collapse and heart failure, brought on by the cumulative action of emetin. The autopsy findings showed only slight anatomic changes.

Discussion. In 1916 Levy and Rowntree⁶ reported the first case of fatal emetin poisoning. This prompted them to investigate the toxicity of various commercial preparations of emetin, by experiments on animals. They found that a daily dose of 5 mg. (3 to 4 mg. per kg.) to be fatal in rabbits in five to six days. Necropsy revealed but slight anatomic changes. The effect of intravenous injections depended on the quantity injected, its dilution, the rate of injection and to a lesser extent on the preparation employed.

This brings up the question as to what the minimal lethal dose of emetin may be. Vedder⁷ reported it to be 2.5 mg. per kg. in rabbits, when given intravenously. Walters and Koch,⁸ in their experiments found it to be 5 mg. per kg., and they also demonstrated the cumulative action of the drug. They showed that if one-half the minimal lethal dose were repeated daily subcutaneously, it would be fatal after an amount equivalent to two and one-half times the minimal lethal dose had been given. On this basis, they estimated the minimal lethal dose for man to be 0.06 gm. daily for twenty-one days (1.37 gm.). Guglielmetti,⁹ perhaps, has estimated the dose of the drug more accurately than other investigators. He found it not advisable to go over 0.15 gm. per day for five or six consecutive days, or 0.10 gm. for eight to ten days, or 0.05 gm. for fifteen to twenty days. The intervals between the series should be long. Fatal toxic action is liable with 0.6 gm. at one time, and death is practically certain with 1.2 gm. at one time.

The disparity in the minimal lethal dose in laboratory animals may be noted in the above quotations. Matsuoka¹⁰ has demonstrated with rats, rabbits and dogs, that individual differences exist in determining the minimal lethal dose, and hence, the conclusion of the minimal lethal dose cannot be applied to the human system, after it has been found by animal experimentation. This point has also been stressed by other investigators.

The minimal lethal doses thus far defined as applying to man are not sufficient, as our patient had considerably less emetin, over a

longer period of time, with frequent interruptions in the treatment, and yet had passed the minimal lethal dose a week before death had occurred, the drug not being given during the last week of life. That much larger doses are given I need but quote Smithies³ who, as late as 1928, advised giving emetin 0.02 gm. three times daily, for two days, and after that increasing by 0.02 gm. after each dose until 0.2 gm. are given three times daily. From my own experience this is much too large a dose and far exceeds the minimal lethal doses established by Guglielmetti, Walters and Kock, Vedder or Levy and Rowntree.

Young and Tudhop¹¹ have shown that emetin is a protoplasmic poison, acting equally on all tissues of the body, the actual cause of death being heart failure. Digitalis, or other heart stimulants will not lessen this toxic action on the heart when once it has been established, as was shown electrocardiographically by Berman and Leake.¹² Thus, once we have passed the minimal lethal dose, we are powerless in an attempt to apply an antidote. Fortunately, very few individuals manifest a susceptibility to emetin, for the minimal lethal dose often is not considered, in the course of treatment of amoebic dysentery.

The action of emetin on amoebæ has not been satisfactorily established. Laidlaw, Dobell and Bishop¹³ have experimentally succeeded with a simple liquid medium in killing *in vitro* four strains of *Entamoeba histolytica* in a 1 to 5,000,000 solution of emetin, within four days, provided that the medium did not become too acid. This differed radically from the results of their previous investigations,¹⁴ when they found that emetin exhibited no characteristically high toxicity for amoebæ, and believed that the therapeutic efficacy of emetin was a result of its action upon the host, rather than upon the parasite. Failure in their previous investigations lay in the fact that the egg-serum media of Boeck and Drbohlav had been used. This result confirms the view that the therapeutic efficacy of emetin in human amoebiasis is probably due to the direct toxic action of the alkaloid on the amoebæ. Willmore¹⁵ and others, however, have shown that there remains a considerable group of cases in which emetin is useless, no matter in what form or manner it may be employed. It was for these emetin-resisting forms of amoebæ, that yatren was originally introduced by Meuhlen and Menk.¹⁶

Conclusions. 1. Emetin is a protoplasmic poison acting on the host as well as on the parasite, and there is no established course of treatment with this drug that can be accepted with impunity.

2. The minimal lethal dose of emetin has not been satisfactorily determined for man. Conclusions drawn from laboratory animals are not applicable, due to differences of species and of individual susceptibility.

3. Death due to the cumulative action of emetin can occur without the advent of sufficiently severe symptoms to warn the physician before the minimal lethal dose has been passed.

4. Cases of susceptibility to emetin cannot be recognized in advance, and each case must be considered as a possibly susceptible individual to prevent the occasional cases of fatal emetin poisoning.

5. Emetin in much less than the minimal lethal dose for man is amoebicidal, and emetin in very small doses, with frequent and sufficiently long rest periods, should be employed. Failure on this basis to clear up the infection, indicates emetin-resisting strains of amoebæ, and other forms of treatment must be devised to cure the disease.

6. Our knowledge of the action of emetin on the human system at the present time, is but poorly understood. Neither do we definitely know its action on amoebæ.

7. There is no known antidote for emetin poisoning.

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CAUSES OF DEATH IN CHRONIC INTESTINAL OBSTRUCTION: A STUDY OF NINETEEN CASES.

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STIMULATED recently by several cases of chronic intestinal obstruction with rupture of the proximal dilated bowel, we were led to review all cases of chronic obstruction autopsied in this hospital with especial attention to their mode of termination, for it had become our belief that the commonly taught causes of death in such cases have been given an improper relative importance. Of twelve standard texts of medicine, surgery and pathology, all place the most emphasis upon toxemia of absorption from stagnant fecal contents. Exhaustion and intercurrent infection are also given much prominence as terminal factors. Four of the twelve mention peritonitis, with or without perforation, but only more or less casually, after discussion of other, supposedly more common findings. A search of the *Index Medicus* for the past five years revealed no paper which, by its title, suggested any deviation from what is apparently the accepted belief.

Over a period of twenty-one years (1908 to March, 1929) there have been 1460 autopsies at the Mercy Hospital. Eighteen cases primarily chronic intestinal obstruction were found. If we add 1 case operated upon and now seemingly recovered, it gives us a series of 19 cases. The obstruction in every case was in the large bowel. Fourteen of these were due to carcinoma; 3 to adhesions; 1 was stenotic, following an acute sigmoid diverticulitis; and in one the cause was not reported. When these were brought together the result was radically different from the opinion described above.

The cases may, for our purposes, be grouped in four subdivisions as follows:

Group I. Spontaneous rupture of the dilated bowel above the site of the obstructing lesion, with resultant peritonitis, 9 cases.*

Group II. Leakage, either at the actual site of the lesion or about the site of operative intervention, with peritonitis, 3 cases.

Group III. Peritonitis without local gangrene or perforation, 3 cases.

Group IV. Death without peritonitis, 4 cases.

Comment. From the above it will be seen that the great majority (15 cases) died as the result of a generalized peritonitis, or, as in the one operative case, had a localized peritonitis at the point of rupture. Of the peritonitis cases, 8 and probably one more, showed

* One of these should be considered as probable spontaneous rupture as the actual gross perforation at the site of local gangrene was not surely present before death.

gross rupture of bowel above the obstructing lesion, either the result of pressure necrosis or of torsion and thrombosis of the local vascular supply. Incidentally, the ruptures were always some distance proximal to the lesion, often at the opposite end of the large bowel. Only one was close, being 10 cm. away. In one case three individual perforated areas were found. It is interesting also that in 2 cases of colostomy and 2 of spontaneous fistula, the supposed relief of obstruction was insufficient to prevent peritonitis. Of the remaining 6 with peritonitis, 3 showed definite leakage, while in 3 no gross escape of fecal contents could be demonstrated.

Group IV. represents the 4 of the 19 cases dying without peritonitis. One of them showed generalized metastasis of the *obstructing carcinoma*, 1 died of *bronchopneumonia*, and in the last 2, toxemia of absorption was the only conjecture that could be made, since other findings, save the obstructing lesion, were essentially negative.

Conclusions. 1. In a series of 19 cases peritonitis was, contrary to accepted opinion, by far the most common cause of death; (15 cases) in chronic intestinal obstruction.

2. Local gangrene and rupture of the dilated bowel proximal to (but often distant from) the obstructing lesion, was the most common cause of peritonitis.

3. Colostomy does not always so sufficiently relieve back pressure as to prevent the rupture of bowel, especially in cases of long-standing obstruction.

4. If such patients die of a toxemia, it is usually that of peritonitis or intercurrent infection, rather than the vague toxemia of intestinal absorption.

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REVIEWS.

THE AUTONOMIC NERVOUS SYSTEM. ALBERT KUNTZ, PH.D., M.D.
Pp. 576; 70 illustrations. Philadelphia, Lea & Febiger, 1929.
Price, \$7.00.

IN this book Dr. Kuntz attempts a herculean task and acquits himself well. To tell the complete story of the sympathetic system, its anatomy, physiology, pathology, and relation to disease, would seem an undertaking to tax the resources of a group of authors. And yet the Reviewer, for one, is glad that Dr. Kuntz has had the courage to carry it through single-handed, for he has produced an exceedingly well-rounded, stimulating, and useful book, which has the additional merit of uniformity.

In regard to the anatomy of the autonomic nervous system he speaks with an authority gained from over twenty years of fruitful, original investigation. Furthermore, in dealing with a body system so extraordinarily complicated as this, the function of which is so bound up with the anatomical arrangement, it would seem that only a person steeped in its morphology would be likely to avoid pitfalls in considering its physiology and pathology. The physiologist should welcome the healthy discussion and criticism of many of his cherished hypotheses from a person who is so thoroughly familiar with the anatomy of the system, and who calmly and judiciously applies everywhere his morphological yard-stick.

There is a wealth of worth-while discussion of recent work, with a valuable list of references. Altogether the book is a distinct contribution, and will undoubtedly prove of great value to the clinician, the physiologist, and the anatomist.

E. C.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By LAWRENCE H. SNYDER, Sc.D. Pp. 153; 28 illustrations.
Baltimore: Williams & Wilkins Company, 1929. Price, \$5.00.

THIS book, dedicated to Dr. Hektoen and written by a geneticist, covers all the historical, theoretical and practical phases of blood typing. Considerable attention is given to the interpretation and defense of the theory of multiple allelomorphous heredity as applied to the blood group, especially as this affects parentage and dis-

tribution of types. A very copious bibliography is appended. Many tables, charts and lists are given. The author warns particularly against faulty technique and inadequate family histories.

The book, however, is a reference work for the partly or wholly initiated and is not to be considered as a textbook or manual. This Reviewer would wish that the portion devoted to inheritance were more extensive and supplied with easily understood examples of practical or experimental genetics, for, although himself fairly familiar with modern theories and results, he feels sure that some blood-grouping workers to whom the book would be useful, may not obtain the best results because of the brevity and directness of statement. So too the position of the O factor is not always clear, as the matter is unfolded in the sections on inheritance and relationships, requiring re-reading and back-referencing.

The immunology of isoagglutination is scarcely touched, largely because students of the subject have devoted most time to the agglutinin factors and their inheritance, and because the theory of von Dungern and others of independent paired factors is bound up with the agglutinin part of the reaction. This feature cannot be wholly ignored for the reasons that subgroups are dependent upon dilution and absorption as well as upon antigen, and because human serum may agglutinate the red cells of lower animals.

The technique described is limited to the simple slide method with sera A and B. While this is adequate for the ordinary typing, the Reviewer believes that for the most exact results in general practice of clinical medicine, especially where the recipient is in a delicate condition (purpura, septicemia and so forth), a cross agglutination should be done immediately before transfusion. And for this, the technique (fifteen-minute test or the prolonged one with washed red cells) should be described. This is the more important in the face of the warnings given by Dr. Snyder, that the condition of the donor as to health and diet must be considered. The section devoted to transfusion does not reflect a full medical viewpoint nor are the technical directions clear enough for the beginner to use.

In regard to the confusion arising from the use of the three systems of terminology—Jansky, Moss and Landsteiner—the author adopts the lettering system of Landsteiner because it affords the easy separation of the major component of the reaction, the agglutinin, and permits clearer comparison with theories and work in inheritance. It is to be hoped that many medical men, especially surgeons, will be persuaded that the lettering system will be better than the arbitrary numbers. It has a better biological and numerical basis.

While warning against conclusions at present on the relation of certain diseases to blood types, the author urges further studies in all lines provided the technique and family history be accurate.

The ethnologic distribution and possible relationships in terms of blood groups are most interestingly told, but because of the yet

controversial character of the question, they do not lend themselves well to review at this place. The Reviewer would wish that another printing type had been selected by the publishers because the shape and spacing of the letters are not conducive to rapid reading. The figures and tables (except the last, which is too crowded) are entirely satisfactory.

H. F.

DIE MENSCHENTHYMUS IN GESUNDHEIT UND KRANKHEIT, TEIL II, DAS ORGAN UNTER ABNORMALEN KÖRPERVERHÄLTNISSEN. By J. AUGUST HAMMAR. Pp. 1114; 815 illustrations. Leipzig: Akademische Verlagsgesellschaft M. B. H., 1929.

THIS is the second part of Professor Hammar's monumental work on the thymus, and deals with the structure of this organ in various diseases. The first part treated of the thymus in the normal condition, and has already been reviewed in this journal (1928, 175, 413). In the present substantial volume are considered over 800 clinical cases, arranged according to the disease which was the cause of death. The same methods of recording the data are used as in the previous part. In each case are given weight and dimensions of the organ, with a low-power view showing relative amounts of cortex, medulla and interlobular connective tissue. There are tabulations of the results in each group. The thymus itself is relatively seldom the seat of pathological processes, so that this is a study of the reactions of the thymus, secondary to these various diseases. These changes show themselves chiefly as quantitative deviations from the normal, rather than qualitative. There is a comprehensive bibliography of 16 pages. This achievement of Professor Hammar comes at the end of twenty-five years' study, and is a great storehouse of information, obtained by quantitative methods, of the behavior of the thymus in various morbid states.

W. A.

THE IMMUNOLOGY OF PARASITIC INFECTIONS. By WILLIAM H. TALIAFERRO, PH.D. Pp. 414; 28 illustrations. New York: The Century Company, 1929. Price, \$6.00.

THIS volume presents a critical review of the mass of immunological work that has been done on infections with animal parasites. Introductory discussions of parasitism, parasitic infections, and immunological methods are followed by chapters on Serological Reactions, Their Specificity and Efficiency; Antibodies Manifested in Certain Infections with Blood Protozoa; Protective and Curative Action of Immune Serums; Cutaneous Tests; Production of Symptoms; The Cellular Basis of Immunity; Immunity in Parasitic

Infections; and Immunity Reactions in Classifying Parasites. A catalogue of the parasites considered, their common synonyms and hosts is given in an appendix. The text, is supplemented by many useful tabulations of immunological tests and reactions, and a bibliography of over seventy pages. This book offers, for the first time, ready access to an important field of research and can be employed either as a manual or for reference. The author is to be congratulated on this splendid presentation.

H. R.

NURSING IN EMERGENCIES. By JACOB K. BERMAN, A.B., M.D., F.A.C.S. Pp. 160; 109 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$2.00.

THE purpose of the book is to familiarize the nurse with quick, correct measures for the care of the patient in emergencies. The directions are concise, the illustrations are particularly good and the equipment required is simple.

The author briefly and adequately described the method for carrying injured patients, treatment of hemorrhage, shock, electrical, thermal and chemical injuries, drowning, asphyxiation, a résumé of antidotes and treatment for the more common forms of drug poisoning and other emergency measures.

The fact that the book is concise and well organized, yet comprehensive, recommends it as part of the equipment of every nurse.

F. C.

THE STORY OF SAN MICHELE. By AXEL MUNTHE, M.D. Pp. 530. New York: E. P. Dutton & Co., 1929. Price, \$3.75.

To those who, like Osler, feel that books about doctors have a proper place in medical reading and libraries, this autobiography of the Swedish doctor, Axel Munthe, may be heartily recommended. Most entertainingly written throughout, it begins with the author's idyllic dream of his future Capri home, then paints in vivid, forceful strokes some of the high lights of the career of a fashionable, yet unconventional, adventurous practitioner in Paris and Rome. A student under Pasteur, Charcot and Huchard, he successfully combined suggestion with rational medicine in Paris wards and writes about it like an artist and scientist. Gruesome yet compelling details of diphtheria and cholera epidemics alternate with romantic sidelights of practice or colorful descriptions of a pistol duel, a visit to Lapland, or an accident in an Alpine avalanche. Through the narrative runs a golden thread of love of animals, which charms more than an occasionally outcropping egotism repels. In places, too, it is difficult to believe that strict veracity is adhered to, but perhaps there are times when a good story should not be spoiled

for the want of a few facts. The final phase, the life at San Michele, though the least medical, is the most attractive and most sympathetically told of the lot. Fortunate the man of action who can thus preserve his worldly values. E. K.

BIBLIOTHECA OSLERIANA: A Catalogue of Books illustrating The History of Medicine and Science collected, arranged, and annotated by SIR WILLIAM OSLER, BT. Pp. 785. Oxford: At the Clarendon Press, 1929.

It is well known that Osler's lifelong fondness for books became one of his major interests during most of his Oxford period, eventually to be manifested in a collection to illustrate the history of medicine and science. This he had decided as early as 1911 to catalogue in the novel and interesting form that we now see, as eventually completed by the editors W. W. Francis, R. H. Hill and Archibald Malloch. The 7783 items were divided by him into 8 sections: Bibliotheca Prima (1702 items), Secunda (2595), Litteraria (1310), Historica (955), Biographica (296), Bibliographica (537), Incunabula (104), and Manuscripts (102).

Though all are interesting, it is to the Prima that one naturally first turns. Here are grouped in chronologic order books by 67 of the greatest medical scientists through the ages, a group that gives a "bio-bibliographical" illustration of the evolution of science (including medicine), with 33 names in slightly subordinate rôles. Thus Item No. 1 is a 1495 edition of Lucretius' "De rerum natura" (illustrating the beginnings, that is, pre-Egyptian and Assyrian), eight other items follow under this heading, as it were, either other editions, translations, or books about Lucretius. After these come 8 items of or about the book of Genesis. Later "The Greeks," for instance, starts with 9 items on Æsculapius; under Paracelsus are 5 items of his works and 35 of lives and commentaries; and so on. For such a selection, of course, no two authorities would agree, and we note occasional rather surprising inclusions and omissions. Nevertheless all must agree that the selection is a good one and has the added interest of reflecting Osler's personality.

The Bibliotheca Secunda, the largest group of the lot, holds all items that do not fit elsewhere, ranging in alphabetical order from works of ancient times that are not of prime importance to books or even articles by contemporaries and including Osler's own output.

The Bibliotheca Litteraria is a concrete evidence of Osler's interest in the avocations of physicians and his belief that medical libraries should properly include nonmedical works by physicians, and the doctor in fiction as well as strictly medical productions. Here is found the notable collection of Sir Thomas Browne's works, Rabelais, Guy Patin's letters, as well as our own Holmes, Weir Mitchell and similar medical authors.

The historical, biographical and bibliographic sections require no comment, other than that each is noteworthy if considered as one section of a private library. Still more so are the incunabula and manuscripts, fortunately for McGill acquired before the present high prices had been attained. The Introduction on "the Collecting of a Library" and the appendix on "A Record Day at Sotheby's" are first class bits of Osler's para-medical writings, while the frequent footnotes that make a catalogue raisonné of the whole are perhaps the most valuable feature of all in this prince of library catalogues. McGill University may well feel proud and fortunate in possessing the library on which it is based.

E. K.

THE DIAGNOSIS OF HEALTH. By WILLIAM R. P. EMERSON, A.B., M.D. Pp. 272; 51 illustrations. New York: D. Appleton & Co., 1930 Price, \$3.00.

THAT there is need for a book on the diagnosis of health is attested by the fact that despite noteworthy advances in medical science, at least one-third of the population are physically unfit. According to Dr. Emerson the prime requisites for optimum health are: absence of physical defects so that an individual may be free to gain, good health habits, proper social adjustment and normal health intelligence. The results obtained by the Author in his Nutrition Clinics in schools, colleges and large communities prove beyond reasonable doubt that good health may be achieved when minute attention is directed to these factors.

In this day of cults, fads and fancies a book such as this, written in a popular vein by a sane physician is of positive educational value to the laity. It also may be perused with profit by most physicians, particularly since Dr. Emerson has found that their own health intelligence quotient is especially low.

S. L.

BOOKS RECEIVED.

NEW BOOKS.

The Medical Clinics of North America, Vol. 13, No. 5, March 1930, Chicago Number. Pp. 207; 17 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Les Syndromes Douloureux de la Région Epigastrique, Vols. I and II. By RENÉ A. GUTMANN. Pp. 1140; 542 illustrations. Paris: Gaston Doin & Cie., 1930. Price, 200 francs.

Procedure in Examination of the Lungs. By ARTHUR F. KRAETZER, M.D. Pp. 125; 15 illustrations. New York: Oxford University Press, 1930. Price, \$2.00.

* Reviews of titles followed by an asterisk will appear in a later number.

The Epidemiology and Control of Malaria in Palestine. By ISRAEL J. KLIGLER. Pp. 240; 32 illustrations. Chicago: The University of Chicago Press, 1930. Price, \$5.00.

A detailed report of how malaria control was brought about in Palestine.

*Immunity in Infectious Diseases.** By PROF. A. BESREDKA. Pp. 364. Baltimore: The Williams & Wilkins Company, 1930.

*Reflex Action. A Study in the History of Physiological Psychology.** By FRANKLIN FEARING, PH.D. Pp. 350; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.50.

*The Treatment of Skin Diseases—in Detail.** By NOXON TOOMEY, M.D. Pp. 512. St. Louis: The Lister Medical Press, 1930. Price, \$7.50.

*Die Regulierung des Blutkreislaufes.** By DR. W. R. HESS. Pp. 163; 21 illustrations. Leipzig: George Thieme, 1930. Price, M. 12.

*Human Biology and Racial Welfare.** By various contributors. Edited by EDMUND V. COWDRY, PH.D. Pp. 612; 54 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$6.00.

*Normal Facts in Diagnosis.** By M. COLEMAN HARRIS, M.D., and BENJAMIN FINESILVER, M.D. Pp. 247; 42 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$2.50.

*Trauma Disease, Compensation.** By A. J. FRASER, M.D. Pp. 524. Philadelphia: F. A. Davis Company, 1930. Price, \$6.50.

*Modern Otology.** By JOSEPH CLARENCE KEELER, M.D., F.A.C.S. Pp. 858; 105 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$10.00.

*Oxford Monographs on Diagnosis and Treatment. Vol. VII. Variations in Blood Pressure and Nephritis.** By HERMAN O. MOSENTHAL, M.D. Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 184. New York: Oxford University Press, 1929.

Oxford Monographs on Diagnosis and Treatment. Vol. VIII. Diseases of the Liver and Biliary Tract. By JOHN PHILLIPS, M.B.* Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 539; 58 illustrations. New York: Oxford University Press, 1930.

Oxford Monographs on Diagnosis and Treatment. Vol. IX. Diseases of the Blood. By THOMAS ORDWAY, M.D. and L. WHITTINGTON GORHAM, M.D.* Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 605; 33 illustrations. New York: Oxford University Press, 1930.

NEW EDITIONS.

Textbook of Pathology. By DKIRENDRA NATH. BANERJEE, M.B. (CAL.), M.D. (BERLIN). Pp. 646; 305 illustrations. Second edition. Calcutta: The Medical Bureau, 1929.

The inclusion of extensive sections on bacteriology, parasitology, diagnosis, etc., has made it impossible to treat any of these sections of pathology itself in an adequate manner.

Medical Gymnastics and Massage in General Practice. By DR. J. ARVEDSON. Pp. 298. Third edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, \$2.50.

Venereal Disease. Its Prevention, Symptoms and Treatment. By HUGH WANSEY BAYLY, M.C. Pp. 242; 77 illustrations. Fourth edition. Philadelphia: F. A. Davis Company, 1930. Price, \$3.50.

The Normal Diet. By W. D. SANSUM, M.S., M.D., F.A.C.P. Pp. 134. Third edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$1.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

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Experimental Transmission of Endemic Typhus of the Southeastern Atlantic States by the Body Louse.—MOOSER and DUMMER (*J. Inf. Dis.*, 1930, 46, 170) call attention to the fact that endemic typhus in the Southeastern states has been recognized apparently only within the last few years. This mild typhus does not depend upon imported cases, but it was shown through cross-immunity tests that the typhus of Europe and the typhus of these Southern Atlantic States are indigenously identical and that they must have a common origin with tarbardillo of Mexico. As a result of epidemiologic studies previously made, the conclusion had been reached that the disease is not transmitted by *Pediculus humanus*. For the purpose of the present experiment, the virus of Maxcy was put in contact with body lice reared on healthy persons in Cincinnati, where typhus is not known. The lice were then fed on a person immune to typhus. Ten days later they were emulsified and injected into the peritoneal cavity of guinea pigs and white rats. The results in all experiments were decisive. All of the lice became infected with *Rickettsia prowazeki* and the inoculation of the rice emulsion of the experimental animals was followed by the typical picture of endemic typhus. As a result of these experiments, the louse must be incriminated as a possible vector of typhus fever.

Blood of Normal Young Women Residing in a Subtropical Climate: Red Cells, Hemoglobin, Volume of Packed Red Cells, Color Index, Volume Index and Saturation Index.—A year ago there was reported by Wintrobe and Miller a study of the blood in one hundred apparently normal young men living in the extreme South. This work has been complemented by WINTROBE (*Arch. Int. Med.*, 1930, 45, 287) in a study of fifty young women living in the same locality. The work was

undertaken as part of the study to determine normal blood standards and partly to determine whether or not an anemia due to climate actually exists. In this study the young women were normal female students who had had a physical examination within a year. All these women had lived in Louisiana, Mississippi and Alabama for three years. The methods of study and the technique of the blood counts are similar to those carried out with the young men. The average red cell count was found to be 4,930,000 per c.mm., 76 per cent of the subjects having counts ranging between 4,640,000 and 5,220,000. The average amount of hemoglobin was 13.76 gm. per 100 cc. of blood. The average hemoglobin coefficient was 13.97 grams and the average volume of packed red cells was 39.55 cc. per 100 cc. The average volume coefficient was 40.3 cc. The author concludes from his work that the results negate the generally accepted idea that there is an anemia in those who live in subtropical countries.

SURGERY

UNDER THE CHARGE OF

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Small Round-cell Sarcoma of the Bladder with Review of the Literature.—MACKENZIE (*Brit. J. Urol.*, 1929, 1, 359) writes that round-cell sarcoma of the urinary bladder is extremely rare and very seldom is more than one case seen in any one clinic. The symptoms are not different from those of any other malignant tumor of the bladder. The diagnosis is usually made by the pathologist either from a snipping or from the surgical or autopsy specimen. Metastases may occur in the regional lymph glands, but remote metastases are late and rare. Wide radical excision of the tumor is the only cure; less radical operations lead to an early local recurrence. A cure by either radium or Roentgen ray treatment has not been reported as yet. Operative results as shown by this series are extremely poor, death following shortly from continued hematuria or toxemia in the great majority of cases. One case has been cured by early radical excision. The author's case suffered from recurrence seven months after operation, but is well now four months after his second operation.

The Effect of Cholecystenterostomy on the Biliary Tract.—GATEWOOD and LAWTON (*Surg., Gynec. and Obst.*, 1930, 50, 40) state that the results of this series of experiments show again that infection of the gall bladder, liver and bile tracts follows cholecystogastrostomy in dogs. In this series, as contrasted to their previous series in which the common ducts were ligated and divided, there is no dilatation of the common ducts and no evidence of gross food particles, or roundworms in the lumina. Infection is definitely less when the common duct is not ligated and

divided. Such experimental differences suggest the following possible explanations for the differences between laboratory and clinical findings. From their previous experiments and from the work of Lehman, the authors had been led to believe that the stoma of a cholecystogastrotomy would close in the absence of common duct obstruction. While in their present series the stomata remained patent, the tendency undoubtedly is for contraction. The gastric rugæ acted almost like valves and probably partially protected the gall bladder from extraneous material. Many animals which were apparently healthy when sacrificed, showed very definite bacteriologic and microscopic evidence of hepatic infection. May there not be silent hepatitis in many of the patients who are clinically well? More autopsy data will probably settle this question. Finally may it not be possible that the human liver is better able to conquer biliary infection than that of the dog? It is a well-known fact that fat metabolism differs materially in the two.

Mortality and End Results of Operation for Abscess of the Lung.—MULLER (*Ann. Surg.*, 1930, 91, 361) writes that lung abscess is a serious disease, and the end result of a group of patients can only be determined a long time after treatment. External drainage of abscess is indicated after failure of conservative measures, in peripheral abscess with pleural involvement; cautery excision or lobectomy is indicated in multiple abscess and in abscess with lobar bronchiectasis. A series of cases is reported with an operative mortality of 28.5 per cent and a final mortality of 40 per cent. Fifty-six per cent of the survivors are clinically well. Two patients recovered from abscess, but still have the cough they had for many years, giving 64 per cent of satisfactory results in the survivors. Those patients who survive the operation, but who do not get permanently well, will be likely to succumb to the effects of the disease. Perhaps an increased use of the cautery method of extirpation of the diseased area done early may result in a greater percentage of ultimate cures, even though the immediate mortality may be higher.

THERAPEUTICS

UNDER THE CHARGE OF

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Different Preparations of Bismuth in Syphilis Therapy.—Although bismuth is adopted by syphilologists as a substitute superior to mercury, little is said of the action of the various preparations of bismuth in syphilis. It is a well-established fact, according to LOMHOLT (*Brit.*

Med. J., 1929, p. 887) that a complete cure is attained only after a prolonged course of bismuth therapy. The aim of the therapy should be to introduce into the organism the largest possible quantities without intoxication. The elimination of the metal is rather slow. Intensive bismuth treatment should not be continued long. It is essential that the preparation should be uniformly absorbed. Oral and cutaneous administration are unreliable. Intravenous injection is rather dangerous. The subcutaneously injected bismuth is irregularly absorbed and may cause an abscess. Intramuscular injection is the preferred method. In the different preparations the metallic bismuth content alone is important, provided that the organism can dissociate the bismuth. All bismuth preparations injure the muscle tissue, causing the formation of a small necrosis which is gradually replaced by granulation tissue which more or less prevents the absorption of the preparation used. Watery solutions are effective but rather painful when injected, and the administration has to be repeated frequently. Oily solutions are painless but rather slowly absorbed. Among the various preparations used in oil, bismuth salicylate seems to be one of the best. If watery solutions are selected for administration the preparation preference should be given to compounds of restricted solubility. The oxychlorid of bismuth is one of the best preparations for watery solutions. With particles of a size of 3 to 5 μ it is almost painless and very powerful. If the absorption of the preparation is complete the daily dose of bismuth metal may be fixed at about 0.5 mg. per kilo of body weight. The author used the following method of treatment in 152 cases with fresh syphilis without a single relapse. Neoarsphenamin, in doses of 60 to 70 cg., was given in a series of 5 to 6 intravenous injections and bismuth oxychlorid in watery suspension, in doses of 15 to 20 cg., in a series of 8 to 10 intramuscular injections. The total number of about 18 neoarsphenamin and 60 bismuth oxychlorid injections were given within a period of about two years. By the end of the treatment of the 152 patients only 2 showed a positive Wassermann reaction, 7 a doubtful and 143 a definitely negative test. Each case should receive individual consideration during the treatment.

The Use of Cowpox Lymph in the Treatment of Certain Skin Lesions.
—On the basis of an experience extending back to 1925, GÖRL and VOIGT (*München. med. Wchnschr.*, 1929, 76, 1669) recommend vaccination as a valuable therapeutic measure in a variety of dermatoses which are marked by the development of vesicles. They find it of particular use in the control of the more resistant form of pemphigus, in herpes zoster and in a variety of other forms of herpes. In the majority of cases of pemphigus the results of its use are dramatic, but in the cases of sepsis presenting the clinical picture of pemphigus its administration is usually without avail. It is a striking fact that in cases of pemphigus repeated vaccinations seem to fail in the production of any lasting immunity against smallpox, since each successive vaccination leads to a normal "take." In one case of pemphigus of the eye a boiled vaccine was employed with most satisfactory results. Herpes zoster is controlled in the sense that a further spread of local eruption is promptly checked. The vesicles already present dry up rapidly and above all the neuralgic pain disappears promptly. Both dermatosis herpetiformis

Duhring and acne fail to respond and erythema bullosum is benefited only in a transitory manner. Recurrent herpes, however, shows a marked tendency toward diminution of subsequent attacks under this treatment. The herpes of menstruation is especially promptly controlled.

The Prevention of Acute Cardiac Death.—Reviewing the various instances of acute cardiac death and, from them attempting to establish a method of determining those patients in whom such accident is prone to occur, MORAWITZ and HOCHREIN (*München. med. Wchnschr.*, 1929, 76, 1075), find that the conditions of coronary sclerosis, syphilitic aortitis and old chronic myocardial disease are those most frequently resulting in sudden death. The electrocardiographic changes indicative of bundle branch block and arborization block, as well as possibly the inversion of the *T* waves in two or more leads and the occurrence of upward convexity of the *ST* line, are also significant forewarnings of sudden death. Very frequent premature ectopic beats, especially in elderly patients with chronic myocardial degeneration, also are of prognostic import. Although it is not usually possible to prove the contention, it seems more probable that such deaths are due to the sudden inception of ventricular fibrillation. Acting upon this assumption the authors have employed as a routine procedure the administration of two doses daily of 0.1 gm. each of quinidin alkaloid. Upon this régime carried out over one year they seem to have reduced the frequency of sudden death to a very marked degree; thus in the year 1927 there were 19 sudden deaths in patients proved, at autopsy, to have had coronary sclerosis or luetic aortitis, none of these patients having received quinidin. During 1928 only 7 patients died suddenly of coronary sclerosis or luetic aortitis. The authors feel that the results of this effort do not justify final conclusions but that they are strongly suggestive of the possibility of working out a fairly satisfactory preventive treatment.

PEDIATRICS

UNDER THE CHARGE OF

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Idiopathic Anemia of the Newborn Infant.—HAPP (*Arch. Pediat.*, 1930, 47, 171) reviews cases in the literature as well as one of his own, and remarks on the similarity in the clinical factor with varying degrees of severity. These babies are born at full term and the delivery is usually normal. In some cases pallor is noted at birth or is seen during the first few days of life with a tendency to increase. This pallor is the only striking symptom and should lead to an examination of the blood. Blood study shows an actively regenerating anemia with marked reduction in red cells and hemoglobin. The white cells are usually increased in number and the differential count is normal. There may be present myelocytes. The platelet count is normal. Active regeneration is evidenced by nucleated red cells, polychromatophilia and increase in

reticulated cells. The spleen is usually slightly enlarged but there is no other glandular increase. There are no constant findings. Icterus is variable. Fragility tests have not been made in all the cases reviewed, but in one case where this test was made, the fragility of the red cells was found increased. Untreated cases have recovered during the first year. Those treated by blood transfusions have recovered more quickly. In the author's case, recovery occurred in seventeen weeks. In none of the cases observed were there any remissions during infancy, and several of the cases had been observed for three or more years. The etiology of this condition is obscure. Tuberculosis in the mother has been mentioned as a possible factor, but of the cases reviewed, the one referred to in this paper is the only one in which this condition has actually been present. There was no anemia in the mother in any of the cases reviewed. The author feels that as a result of some unknown factor the hematopoietic function is depressed in these newborn infants and this factor is probably operative during intrauterine life. No conclusive evidence of hemolysis can be shown in these anemias. Rapid degeneration has been seen and it would seem that the hematopoietic function is definitely stimulated by blood transfusion which is suggested as the treatment of choice together with the administration of organic iron in broths and liver.

The Antirachitic Value of Irradiated Wheat.—TISDALE and BROWN (*J. Am. Med. Assn.*, 1930, 94, 854) made interesting studies on the influence of this irradiated product upon rats and they attempt to interpret the results from the standpoint of the practicing physician. They feel most positively that irradiated wheat is not a reliable source of vitamin "D" as is cod-liver oil or irradiated ergosterol. The antirachitic potency is not sufficient entirely to prevent and certainly not to cure rickets in the amounts consumed in the average diet, therefore, they recommend that, in addition should receive cod-liver oil or viosterol. This need of an accessory source of vitamin "D" raises the question as to the value of irradiated wheat as a source of vitamin "D." In answer, the authors state that cereals are used largely for their energy-producing value and experience shows that rickets develops in its most severe forms in those infants fed large amounts of cereals and other carbohydrates. In other words cereals should be regarded as rickets-producing foods and irradiation can change them from rickets-producing foods to rickets-preventing foods, and in this lies the value of the irradiation as now performed. As three teaspoonfuls of cod-liver oil each day during the winter months do not furnish any excess of vitamin "D" of the amount necessary to prevent rickets in the average infant or young child any means that can remove the rickets-producing tendency of cereals should be of value.

New Experiences with Diphtheria Vaccination.—POCKLES (*Deutsch. med. Wchnschr.*, 1930, 56, 46) states that among the children of Berlin who had been vaccinated against diphtheria a considerable number contracted the disease, and in some there was a fatal outcome. He thinks that this failure of vaccination is due to the fact that instead of effective subneutralized toxin antitoxin, other vaccines were used. The subneutralized toxin antitoxin was originated by von Behring and this is the product commonly used in America. In Germany its use has been

discontinued on account of the frequency of local reactions. In its place Schmidt's toxin antitoxin floccules, or a neutral toxin antitoxin have been used because these do not cause reactions. According to the author, children vaccinated with either of these two did not always develop a sufficient quantity of protective substance. He vaccinated 36 children with toxin antitoxin floccules and 13 with a neutral mixture of toxin antitoxin. He later determined the antitoxin content of the blood and it was found that only a part of the vaccinated children had a quantity of antitoxin that is necessary for protection against diphtheria. Because of the insufficiency of these two preparations the author reserved—for use in diphtheria toxoid, a toxin that is modified by treatment with formaldehyd. The advantage of this preparation is claimed to be in the fact that it does not contain antitoxin and consequently is free from heterologous serum and thus cannot cause anaphylaxis. A disadvantage of this toxoid is that it causes local reactions, especially in older children or in adults. Another objection is that the subcutaneous injection has to be repeated three times. This method has brought good results in many countries and is suggested as being worthy of consideration. Passing to the Schick test, the author points out that because it indicates the presence of minor quantities of antitoxin that are not sufficient for protection, it is not always a reliable indicator for immunity.

Symptoms of Vagotonia and Thymic Hypertrophy.—ALDRICH (*J. Am. Med. Assn.*, 1930, 94, 1119) reminds us that the vagus is a part of the parasympathetic or bulbosacral division of the autonomic system and that its activity is normally opposed by the sympathetic division of this system. Theoretically vagotonic symptoms may be produced either by stimulation of the vagus or the parasympathetic, or by a reduction in the activity of the normal antagonist, the sympathetic. Activity of the suprarenals has a marked effect on the autonomic system, therefore vagotonic symptoms might follow diminished suprarenal activity. In this connection Marine pointed out that spontaneous involution of the cortex of the suprarenals occurs during the first two weeks of extrauterine life. He and other experimentors have produced by suprarenalectomy, conditions similar to status lymphaticus with thymic enlargement, and since status lymphaticus has been associated clinically with reduction in the suprarenal chromaffin substance, Marine suggests a significant relationship. He also assumes a close relationship to status lymphaticus as due to a lack of the epinephrin hormone in the blood which makes adequate systole of the heart and bloodvessels impossible, and points out that in death from this cause the heart is always in diastole. The report of MacLean and Sullivan is quoted, emphasizing an extremely low blood sugar in three cases dying from status lymphaticus. They hold that such a condition might result from imperfect suprarenal response to the various strains imposed on the body none will result in death in this condition. In this study the author analyzed 40 patients and he felt that the symptoms exhibited by them can be explained on the basis of spasm of smooth muscle and the vagus control and the suprarenal involution occurring in the newborn may result in both vagotonia and thymic hypertrophy. In his series of patients irradiation over the thymus seemed to be effective in relieving the symptoms.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Hypersensitiveness to Arsphenamin in Guinea Pigs—Experiments in Prevention and in Desensitization.—SULZBERGER (*Arch. Dermat. and Syphilol.*, 1929, 20, 669). Following the investigations of W. Frei, working on the sensitization of guinea pigs with arsphenamin, the author conducted a similar series of observations to determine the sensitization mechanism in arsphenamin as a representative of the chemical group as a whole. Twenty-three guinea pigs were prepared by an intradermal injection of arsphenamin. Six of the animals received one-third of the minimum lethal dose of arsphenamin intracardially twenty-four hours after the intradermal injection. A skin hypersensitivity to arsphenamin could be observed in 16 of the 17 animals that received no intracardial injection of this kind. This hypersensitivity showed itself in 12 animals by a flaring-up of the area of injection from six to fifteen days later, and in 16 hypersensitive animals by a reaction of hypersensitivity to a second intradermal injection of arsphenamin. The second intradermal injection was administered to all the animals as a skin test thirty-one days after the first injection. In contrast to those which received no intracardial injection, the animals that had received an intracardial injection of arsphenamin at no time showed signs of hypersensitivity, in the form either of a flare-up or reaction of hypersensitivity to the skin test. The reaction of hypersensitivity differed greatly from the flare-up due, in the belief of the author, to variations of degree occurring at different times in the course of the same hypersensitivity. A second series of experiments was conducted in which the author attempted to desensitize 12 previously sensitized guinea pigs by intracardial injection fourteen days after the intradermal preparation of the arsphenamin. Of these animals, 6 received intradermal injections of arsphenamin identical with that which had achieved the prevention of sensitization when administered after twenty-four hours in the earlier experiment, while the other 6 animals received an intracardial injection of gold sodium thiosulphate. Neither of these measures was effective in desensitizing the guinea pigs and they reacted to subsequent intradermal tests with arsphenamin fully as strongly as the sensitized but not intracardially treated controls. The author emphasizes that his failure to produce desensitization does not prove its impossibility but rather that the method must be varied in further experiments. The author proposes to apply his results in guinea pigs

to the analogous conditions in human beings which include the occurrence of dermatitis following the more or less intimate contact with chemicals and the toxicodermata from drug ingestion. The author points out that his results confirm the clinical findings of previous investigators that patients having had arsphenamin dermatitis react to intradermal tests with arsphenamin much more strongly than normal persons. He agrees with Klauder that in a great many cases arsphenamin dermatitis follows an infiltration of cutaneous and subcutaneous tissues with arsphenamin and that as a practical application an effort should be made immediately to complete an injection in which such leakage occurs by the correct intravenous route. It might even be advisable to give the succeeding intravenous injection of arsphenamin in such an instance at a shorter interval than usual. The author concludes that all tests agreed much more closely in nonsyphilitic than in syphilitic cases so that a negative reaction given by any of the tests is of more value in ruling out syphilis than is a positive reaction of value in indicating syphilis.

(The word arsphenamin is used by the author to mean neo-arsphenamin.)

The Chemistry of the Blood in Diseases of the Skin.—SCHAMBERG and BROWN (*Arch. Dermat. and Syphilol.*, 1930, 21, 1). In a series of 875 patients with miscellaneous dermatoses, the authors found no appreciable changes in the figures for blood sugar. A retention of non-protein nitrogen, urea nitrogen and uric acid was discovered in 22.6 per cent to 47.7 per cent of their cases of eczema and pruritus (generalized). This increase of the nitrogenous constituents of the blood is due mainly to an improper diet or to some form of renal dysfunction such as a low-grade interstitial nephritis. The fact that this occurs more often in subjects who are in middle life or older favors this view. There is a normal pronounced discrepancy in the nitrogenous figures between the sexes which the author believes is partly accounted for by a general difference in diet. A study of the blood chemistry of patients with refractory dermatoses is of material aid in prescribing appropriate dietaries.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Pseudomyxoma Peritonei of Ovarian Origin.—The peritoneal neoplasm composed of pseudomucinous material, called pseudomyxoma peritonei, which is usually due to a ruptured ovarian cyst is of interest

to every gynecologist but is seldom seen in the practice of any one man. Thirty cases of this type have been observed in an eighteen year period at The Mayo Clinic as reported by MASSON and HAMRICK (*Surg. Clin. of N. America*, February, 1930, p. 61). The largest number of cases was found in patients in the sixth decade, while 80 per cent of the patients were past the age of forty years. Swelling of the abdomen and pain are the two most constant symptoms and their average duration before operation was less than a year. On examination the pelvis and abdomen are usually found to contain one or more masses. A large tense abdomen with a fluid wave of a questionable character may be the only abnormality found. They found a higher percentage of bilateral involvement in patients with ruptured pseudomucinous cystadenomata than in patients with the same type of unruptured tumors. This bilateral involvement was most marked in cases of malignant lesions and when papillomas were present. Pressure phenomena from the mucilaginous tumors play a large part in the health of patients with this disease, while pulmonary embolism and general peritonitis were the chief factors in the operative mortality. The prognosis is naturally better in cases of benign lesions. Removal of both ovaries and the appendix is urgently indicated in women who have passed the menopause. In those who have not passed the menopause it is generally desirable to save one ovary, but the surgeon should take into account the type of growth in the affected ovary. Hysterectomy is indicated in some cases, resection of the omentum in others and as much of the gelatinous material as possible should be manually removed from the abdominal cavity at the time of operation. At times the bowel and even the uterus may be perforated by the pseudomucinous tumors so that the extent of the operation will have to be decided by the type of lesions met. They believe that all cases should receive postoperative treatment by Roentgen ray and radium.

Irradiation of Vulvar Cancer.—We are inclined to agree with DE BÜBEN (*Surg., Gynec. and Obst.*, 1930, 50, 110) of Budapest when he states that the treatment of cancer of the vulva is a most arduous task. Of the methods of treatment at our disposal he ranks radiotherapy first, not only because it can be used in advanced cases, but also because in most instances its use improves the condition or at least ameliorates the suffering and in a few cases even permanent cure has been secured. In most cases radiotherapy produces a temporary improvement and delays death; at any rate the life of the victim is made tolerable. Of 31 patients with vulvar cancer treated with radium at his clinic, 2 were free from recurrence six years later. One lived four years after treatment, 2 lived three years, 3 lived two years, 5 lived one year, 7 died within one year and in 7 the duration of life is unknown. After excision and microscopic diagnosis, patients with cancer of the vulva to be treated with radium are given a single dose amounting to 1200 to 2400 mg. element hours, if possible. Then if at control examination the effect seems to be unsatisfactory, the radium treatment is repeated in six to eight weeks. For irradiation of the lymph glands he uses Roentgen rays, a pigmentation dose being applied three times at intervals of six weeks. Patients treated with radiotherapy are instructed at the end of treatment to return for examination every three months, later

every six months. While these results are not startling it is well to remember what can be accomplished by nonoperative means, as in many cases the patients who are afflicted with this type of cancer are far from being in a satisfactory general condition to withstand the prolonged operation which is necessary to radically remove the cancer together with the regional lymph nodes.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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A Case of Abscess of the Iris.—Abscess of the iris is so rare that it is not even described in such a textbook as Fuch's. Therefore Jadavji Hansraj (*Indian Med. Gazet.*, 1929, 64, 510) reports in detail a case recently seen in Bombay. A man, aged thirty-five years, came to the hospital complaining of pain and redness in the eye, the only cause that he could give being that he had rubbed his eye with a coarse cloth six days before. Examination showed marked ciliary injection, photophobia and lacrimation, the ciliary injection being much more marked on the side of the abscess (temporal). The cornea was absolutely clear. The temporal half of the anterior chamber was occupied by an oval, yellowish-white substance, immobile either to change of position by the patient or to pressure. The temporal half of the pupil and the portion of the iris peripheral to it was covered by the mass in the anterior chamber. Such of the iris as could be seen was slightly muddy, the crypts on the anterior surface were obliterated and the pattern was lost. The ocular tension was above normal. Vision was finger counting at one foot only; the other eye had full vision. A diagnosis of lens dislocated into the anterior chamber was made because of the color and appearance of the mass, the shape and size of it, and the increased intraocular tension with signs and symptoms of secondary glaucoma. Operation incision in the outer half of the cornea to remove the supposed lens. As soon as the anterior chamber was opened muddy colored pus together with a little aqueous humor began to ooze and the mass began to disappear. When irrigated it was found that the pus was coming from an opening in the iris. The outer layers of the iris were changed to a muddy color and formed a thin capsule for the sac which contained the pus. The eye was bandaged and treated with atropin. In addition the patient was given three injections of 100 cc. of a 1 per cent solution of mercurochrome on alternate days. The iris cleared completely except for posterior synechia. Vision is gradually improving; at present, finger counting at 4 feet. The infection must have been endogenous, probably arising from pyorrhea alveolaris; rubbing the eye traumatized the iris and an abscess, instead of mild iritis resulted.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Psychologist's Interest in Hearing.—"In the modern science of life the living organism has gradually revealed a greater and greater complexity—a complexity of substance as well as of function. So complicated have the body and its operations become that all who delve into its fascinating intricacies are inclined to alternate between the ardent enthusiasm of the explorer and the bewildered doubt of the lost traveler. . . . In the sciences of life problems seem, therefore, to approach solution not so much by the discovery of new simplicities as by the revelation of new but enlightening subtleties." Stating that *hearing* is but a special case of the general trend, BENTLEY (*Arch. Otolaryngol.*, 1929, 10, 282) calls attention to the fact that the particular focus of the psychologist is set on the experience of hearing sounds. The approach to this experience of hearing is considered by the author under four main headings: (1) A description of the simpler auditory experiences; (2) the relation of these experiences to the forms of energy delivered to the cochlea; (3) the relation of them also to aural structures and mechanisms, and (4) an account of various more complex auditory phenomena. The individual importance of the various fields in biologic, clinical and psychologic research is recognized; and the necessity for a common understanding and close coöperation between them is stressed.

The Localization of Sound.—"The word 'localization' as applied to sound is of psychological rather than physical origin. It deals with a sensation more than with a physical measurement. It differs from *location* in that it does not fix the position of a source of sound." Stating that with our unaided listening equipment we can obtain only a sense of direction, TUCKER (*J. Laryngol. and Otol.*, 1929, 44, 812) calls attention to the fact that the head, as normally placed, is best adapted for listening in a horizontal plane. Sound localization is most accurate in front, nearly as accurate for the back, and least accurate at the side and for the overhead position. Normally, localization occurs by virtue of some difference in stimulus received by the two ears. There are three ways in which such variation in stimulus can arise: (1) Difference in sound intensity; (2) difference in phase of the incoming sound waves, and (3) difference in time of arrival of some corresponding portions of the sound waves received by the two ears. After discussing these theories, the author mentions certain aural methods by instruments devised for sound location of aeroplanes.

Further Experience with the Dichloramin Treatment of Mastoid Wounds.—FENTON (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 657) concludes that bacteriologic examination bears out eleven years of

clinical experience in several hundred cases, demonstrating the value of dichromin-T, 2 per cent in chlorcosane, as a routine dressing in acute mastoid surgery—not only for its remarkable inhibitory action on bacterial growth but also for shortening materially the duration of postoperative treatment. The wound is left open, save for one or two sutures at the ends. It is filled with the oil which is “held in” by a lightly inserted fold of narrow oil-soaked gauze packing. The dichloramin is used daily during the first week or ten days of the reparative process.

Deafness in Syphilis: An Audiometric Study.—In a series of 2201 thoroughly studied patients on a general diagnostic service in which emphasis was laid on diseases of the ductless glands, about one-half could be classed in the nonendocrine group and more than one-third (792) were subjected to audiometric study. DRURY (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 625) after an exhaustive analysis of these 792 cases, found that 81, or practically 10 per cent, of them showed a curve characterized by a marked lowering of auditory acuity at 4096 d. v.; and that in this group there was a surprising incidence of “putative or established syphilis.” Emphasizing that the recognition of syphilitic auditory neuritis is of paramount importance as possible evidence of early cerebrospinal involvement, the author recommends the audiometer as the instrument of choice in the diagnosis of incipient syphilis of the auditory nerve. He further states that when this particular curve—the “dipper gap”—is encountered in a syphilitic, the aural damage is permanent, although the etiologic factor may be cured successfully.

RADIOLOGY

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Etiology of the Ill Health of Children Born After Maternal Pelvic Irradiation.—The cause of ill health or defects manifested by 38 or 50.7 per cent of a group of 75 children irradiated while *in utero* has been investigated by GOLDSTEIN and MURPHY (*Am. J. Roent. and Rad. Therap.*, 1929, 23, 322), who have reported previously the effects of preconception irradiation. The ill health of 10 children of the 38 was attributed to parental influences or to accidental causes. Twenty-eight, or 37.3 per cent of the 75 children born after postconception radium or roentgen irradiation manifested mental or physical abnormalities which could not be attributed to parental influences, accidental infections, or causes other than irradiation. In this group of 28 children there were 20 who suffered severe disturbances of the central nervous system. Sixteen microcephalic children were included in this group. The remaining 8 children exhibited other serious disturbances of health

and development which may have resulted from the irradiation received while *in utero*. The large number of grave malformations appearing in children born after postconception irradiation, the uniformity of these deformities (chiefly microcephaly and mental defects) strongly indicate that there is a distinct relation between the irradiation and the defects. The occurrence of two cases of microcephaly and one of hydrocephaly in children born of women irradiated after the fifth month indicates the danger of irradiation of the fetus in the advanced stages of development. It is the belief of the writers that therapeutic pelvic irradiation during pregnancy is extremely likely to injure the growing embryo, and may result in the birth of a seriously defective child. On the other hand, they find no indication that irradiation for diagnostic purposes during pregnancy is deleterious in any way to the health of the offspring.

Treatment of Malignant Tumors of the Rectum by Radium and Roentgen Rays.—BOWING, FRICKE and SMITH (*Radiology*, 1929, 13, 443) report the results in 127 cases of malignant disease of the rectum treated at The Mayo Clinic with radium and Roentgen rays. The majority of the cases were inoperable, due to the size and extent of the primary lesion, or local metastasis, metastasis to important viscera or patient's poor general condition. Adenocarcinoma of moderate malignancy predominated. Twenty-three per cent of the patients lived from three to six months, 18 per cent from six to nine months, and 34 per cent longer than nine months. Almost 4 per cent survived eighteen to twenty-four months, and slightly less than 3 per cent lived twenty-four months or more. The writers regard it as evident that the lives of these patients were prolonged and that the activity of the disease was reduced thus diminishing distressing complications. Improvement noted consisted largely in lessening of rectal discharge and pain, reduction of the size of the tumor and cessation of bleeding.

Influence of Phenolphthalein on Intestinal Movements.—From their roentgenologic studies CALDWELL and CRANE (*Radiology*, 1929, 13, 403) offer the following conclusions: Phenolphthalein in ordinary dosage has no appreciable effect on the movements of the stomach or the small intestine. Phenolphthalein does not directly affect the rate of movement, in any part of the digestive tract, of the food material taken simultaneously with it. The proximal half of the colon shows very little, if any, increase in its motor activity during the period in which phenolphthalein is most active, about eight to twelve hours after it is taken. The movements of the distal half of the large intestine are strongly stimulated by phenolphthalein during its active period. Phenolphthalein has no local effects in any portion of the alimentary canal due to chemical or mechanical action on the bowel wall. The drug is in part absorbed during its passage through the small intestine and re-excreted into the colon or large bowel. The laxative properties of phenolphthalein are due chiefly if not entirely to a stimulation of the large bowel by that portion of the drug which is absorbed and carried by the blood to this portion of the tract. Only that portion of the intestinal contents which has reached the distal colon by the time the phenolphthalein becomes active, namely, about eight to twelve hours after its ingestion, is directly influenced by it. Other apparent effects are secondary and indirect.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Etiology of Epidemic Encephalitis. Its Relation to Herpes, Epidemic Poliomyelitis and Postvaccinal Encephalopathy.—LEVADITI (*Arch. Neurol. and Psychiat.*, 1929, 22, 767) reviews in very clear sequence the modern researches in relation to the etiology of epidemic encephalitis and its relation to herpes. He feels that his own researches have established the following facts: Inoculation of laboratory animals with encephalitic material by the most various routes surprisingly seldom gives positive results; direct transmission of the virus from man to animal has been secured only in the rabbit; after successful transmission to one rabbit the virus can be maintained successfully by regular passages through the animals of the same species; he believes also that his previous researches had seemed to clear up some of the characteristics of the encephalitic virus, the clinical and anatomopathologic aspect of the infection in the various receptive species, the routes by which the virus penetrates, its distribution in the organism, how it is eliminated, immunity, the problem of germ carriers, and some other points. Following this period in the research the author was successful in producing keratitis by corneal inoculation which gave rise also to typical clinical and pathologic pictures of experimental encephalitis. Prior to 1920 certain German research workers by experimenting with herpetic keratitis came to the conclusion that herpes was a specific infectious disease produced by a virus which was probably invisible and filtrable and was virulent for the rabbit. Later Doerr and Vöchting observed disturbances similar to encephalitis in rabbits in their experimental animals suffering from herpetic keratitis, thus demonstrating an invasion of the central nervous system by this virus. This led to the conception of the identity in nature of the virus of encephalitis and the virus of herpes. The author gives the credit for this to Blanc. Experiments in cross immunization were then undertaken and led to the conclusion that the two viruses were either identical or very similar, the chief differences being on the one hand a greater cutaneous affinity and on the other hand a greater cerebral affinity. Subsequent researches have been both nonconfirmatory and confirmatory. The principal objections to the nonconfirmatory researches have been a confusion of epizootic encephalomyelitis in the rabbit with encephalitis produced by the herpetic encephalitic virus. These two conditions can be differentiated clinically and pathologically, hence the majority of the nonconfirmatory experiments can be discarded. The confirmatory researches have established certain encephalitic strains of the herpetic

type as follows: Levaditi and Harvier strains of cerebral and nasopharyngeal origin; the Doerr and Schnabel strain from the cerebrospinal fluid of an encephalitic patient; the Doerr and Berger strain from the neuraxis of a case of epidemic encephalitis diagnosed by microscopic examination; the Berger strain by inoculation of glycerinated encephalon into rabbits; the Schnabel strain from the cerebrospinal fluid of a case of acute encephalitis; the Luger and Lauda strain from cerebrospinal fluid; the Hogander strain from glycerinated encephalon; and some other strains not so fully studied. The author considers his own researches confirmed and that the total researches up to this time lead to the following conclusions: The transmission of encephalitis from man to rabbit is extremely difficult; rabbits that resist the original inoculation are found to be free from lesions and their sensitivity to inoculation from a previously infected animal is as great as that of rabbits not previously inoculated, so that their resistance to the first inoculation is not due to natural immunity; all the strains so far isolated and studied by the author and his collaborators have been keratogenous, are virulent for the guinea pig and the mouse and nonpathogenic for the dog, and cross immunity shows the identity and nature of the strains with the herpetic virus. Hence, the author believes that the virus of herpes as the chief etiologic factor of von Economo's disease has been entirely confirmed. The chief objection to this, he believes to be the contention that the presence of the herpetic virus in the neuraxis of encephalitic subjects is not an absolute proof that it plays an etiologic part in von Economo's disease since it might be a common organism associated with the still unknown virus of encephalitis. The author cites a number of observations that materially reduce the probability of this being the case. In researches as to predisposition and virulence in experiments on monkeys the author found that the monkey is, as a rule, refractory to the encephalitic virus isolated from, and maintained by passages through the rabbit even when the virus is introduced direct into the encephalon. Certain monkeys he found to be exceptions to this rule which he attributes to impairment of their natural resistance. He compares this with observations made on man and believes that simian and human species are not capable of contracting encephalitis unless for special reasons the natural refractory state proper to these species is impaired. On this basis he accounts for the discrepancy between the frequency of herpes and the rarity of encephalitis. Moreover, the author was able to produce typical encephalitis in a monkey by intracerebral inoculation of an herpetic virus. He discusses at length variations in the neurotropic, corneotropic and dermatotropic affinities of the various strains. In conclusion, he does not believe that the etiologic problem of epidemic encephalitis is completely solved, nevertheless, a great deal of progress has been made and the identity of encephalitis virus with that of herpes has been fairly well established.

Habitus Lipodystrophicus with Affective Psychosis—(Hypomanic Excitement).—WERTHAM (*Arch. Neurol. and Psychiat.*, 1929, 22, 714) would reserve the term *habitus lipodystrophicus* for those types (so far found only in women) in which there is a marked incongruity in the fat deposition of the upper and lower parts of the body, usually showing marked thinness above the waist line combined with marked obesity.

below. He reports a case of this type which showed a typical hypomanic excitement. In discussing the case he shows that the patient falls within the upper limit of the pyknic body type but nearer the range of values found in cases which belong to neither the pyknic nor the asthenic group. He believes that the lipodystrophic habitus is constitutionally connected with lipodystrophia progressiva, the etiology of which is as yet unclear, but which seems to have a constitutional pathogenic factor. He comments on the fact that dysplasias of any type are relatively uncommon in affective psychoses and considers the case reported here as of special interest for this reason.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Types of Tubercle Bacilli in Human Tuberculosis.—GRIFFITH (*J. Path. and Bact.*, 1929, 32, 813) reviews much of the English as well as some of the foreign literature and reports the more recent researches of himself and his colleagues on this subject. An analysis of their results is considered in the three age groups of four years and under, five to fourteen years, and over fourteen years of age. In the English series of specimens. of 116 cases of cervical gland tuberculosis 3 were of human, and 18 of bovine origin in the first age group; during the second period 28 were of human and 26 of bovine type; 32 were of human and 9 of bovine origin in the third age group. The total bovine incidence of cervical adenitis at all ages was 45.7 per cent. Among 511 cases of bone and joint tuberculosis 60 were of human and 24 of bovine type during the first period, 277 were of human and 65 of bovine during the second period, and 81 were of human and 4 of bovine origin during the last period. The total bovine incidence in the bone and joint disease group was 18.2 per cent. Of 23 cases of urogenital tuberculosis none occurred under four years; in the second age group 2 human and 1 bovine strain were encountered; after fourteen years of age 17 cases were of human and 3 of bovine origin. The total bovine incidence of urogenital tuberculosis was 17.4 per cent. In 33 cases of meningeal tuberculosis studied, 2 were of human and 1 of bovine type during the first period, 13 of human and 7 of bovine in the second period, while 9 human and 1 bovine strain were met with in the last age group. The total bovine incidence of meningeal disease was 27.3 per cent. Material taken from 183 autopsies yielded 72 human and 29 bovine types in the first age period, 48 human and 7 bovine in the second, and 21 human and 1 bovine in the third. The total bovine incidence in the autopsy group was 22.3

per cent. In the Scottish series of specimens, of 17 cases of cervical gland tuberculosis 1 human and 3 bovine strains occurred in patients under four years, 3 human and 7 bovine between five and fourteen years, and 1 human and 2 bovine after the latter age. The total bovine incidence in this group was 70.6 per cent. Bone and joint tuberculosis occurred in 30 of the Scottish cases, 12 human and 6 bovine strains being represented in the first age group, 8 human and 2 bovine in the second, and 2 human but no bovine in the third. The total group bovine incidence was 26.6 per cent. Considering the distribution of the primary lesions as a criterion it appeared in the author's investigations that the bovine bacillus enters the body exclusively by way of the alimentary tract while the respiratory tract appeared to be the chief portal of entry for the human bacillus. Evidence is advanced to show that demonstrable tubercle bacilli from foci presenting an inactive appearance at autopsy must frequently be dead as inoculation of material from these areas into susceptible animals meets with negative results. Tuberculous lesions whether produced by human or by bovine tubercle bacilli, and wherever situated, may undergo spontaneous arrest and cure.

The Distribution of Colloidal Lead in the Tissues After Its Intravenous Injection.—DILLING and HAWORTH (*J. Path. and Bact.*, 1929, 32, 753) have followed by histologic and chemical methods the fate of therapeutic forms of colloidal lead used by the Liverpool Medical Research Organization in the treatment of malignant disease. The doses, given intravenously, which were injected into cats in divided amounts over a period of three to four hours, were massive, varying between 0.3 and 0.5 gm. lead; while those given to rabbits by a single injection usually represented 0.025 to 0.05 gm. of lead. The authors found the lead concentrated first in the spleen where it had entered the splenic cells, the large phagocytic cells and more rarely the endothelium of the splenic vessels. Large amounts were also found early in the parenchymal and Kupffer cells of the liver and in the alveolar cells of the lung. In animals killed twenty-four hours after an injection, there was less lead in the spleen while particles were present in larger numbers and in more uniform distribution in the hepatic and Kupffer cells. The particles in the lungs, after this period, had largely disappeared from the alveolar walls and were contained in leukocytes in the intra-alveolar septa. No evidence of injury to the liver, lung, or spleen by the lead was observed. In the kidneys the granules were distributed within the glomeruli and around the secreting tubules, less frequently along the collecting tubules. These organs showed microscopically some swelling and degeneration of the secreting cells in the cortical tubules with loss of nuclear staining; in some cells necrosis was apparent. Although the lead was observed to be concentrated chiefly in the cells of the reticuloendothelial system, chemical examination revealed its widespread presence in various tissues. Excretion occurred into the urine, the bile, and the alimentary tract.

Etiology and Pathology of Primary Lung Tumors.—SCHUSTER (*J. Path. and Bact.*, 1929, 32, 799) notes the increasing incidence of lung tumors and reports the investigation of 62 cases of pulmonary neo-

plasm. In this group there were 8 cases of sarcoma, lymphadenoma and thymic tumor and 54 cases of carcinoma. The author classifies the carcinomatous growths as: (1) Tumors arising from the bronchial structures, composed of epithelium which may be high columnar, or spindle in shape, or of polymorphic character including squamous and polygonal cells. (2) Small cell tumors composed of cells of round, oval, cubical, or small columnar shape, probably of bronchial origin and frequently metastasizing to brain. (3) Tumors from the alveoli. The existence of alveolar carcinoma has not been proven. The pulmonary tumors metastasized most frequently to lymph gland, liver, suprarenal gland, and brain, but widespread and numerous metastases were not common. The persistent presence of columnar cells and mucin in the various tumors suggested the bronchial lining as the common site of origin of pulmonary neoplasm but it was impossible to distinguish histologically between tumors which arose from the bronchial epithelium and those which arose from the glands and their ducts. No definite etiologic factor in the incidence of these growths could be demonstrated and pneumokoniosis did not appear to be a cause.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Endemic Typhus Fever of the Southeastern United States: Reaction of the Guinea Pig.—MAXCY (*United States Pub. Health Rep.*, 1929, 44, 589) gives the following discussion and summary after reciting the details of his studies: Blood from persons sick with the "endemic typhus" of Southeastern United States injected into guinea pigs produces a definite febrile illness, with recovery and subsequent immunity to reinoculation. The reaction of the guinea pig appears to be identical with that produced by Mexican typhus, according to Mooser's description. It differs from that of the Old World typhus: (1) in regard to the character of the fever curve; (2) in the relative rarity of the so-called typhus nodes in the histologic preparation of the brain; (3) in the presence of an obvious and well-defined scrotal lesion first described by Neill in 1918 in Mexican typhus. So far as the differences in the temperature curve and in the relative frequency of occurrence of typhus nodes are concerned, these might be explained as due to strain variation. In a study of 13 strains obtained from cases in the same general locality in Poland, Hach (1925, b) found one strain in which, in spite of a very outspoken febrile reaction, the brain lesions were extremely hard to find.

In another the temperature elevations were relatively slight, although the period of incubation and duration of the fever were essentially the same as in other strains. On the other hand, the involvement of the scrotum is much more striking and extensive than has been observed or described in guinea pigs inoculated with Old World typhus. When this obvious involvement was first encountered in a strain obtained from a case in Montgomery, Alabama, in 1925, it was thought possible that it might be due to a secondary or contaminating infection. Since that time the same finding has been present in three other strains which have been successively established from cases in Montgomery, Ala., Savannah, Ga., and Wilmington, N. C. It was observed by Dr. William Allan in a strain from a case in Charlotte, N. C. (personal communication). It has been constantly associated with the presence of the virus and not with other infections in guinea pigs. It has not been observed during the past two years in guinea pigs from the same stock which have been inoculated with two strains of Old World typhus, though much less extensive histologic changes of a similar nature occur. These findings have been so consistent that it seems to be established that the obvious involvement of the scrotum and the rarity of brain lesions are characteristic of the endemic typhus virus in guinea pigs as they are of Mexican virus. The demonstration of rickettsia-like organisms in the epithelial cells of the tunica brings additional evidence as to their identity.¹ It appears, therefore, that a North American strain of typhus can be recognized and distinguished from Old World typhus, though the two be closely related immunologically. The conclusion may be drawn that the disease which is endemic in our eastern seaports, Wilmington, N. C., Charleston, S. C., Savannah, Ga., Jacksonville, Fla., belongs to the typhus group, but is not dependent upon importation from across the sea. This disease has a common origin with the typhus of Mexico, even though transmission be effected by some agent other than that generally recognized for this disease, namely, the louse.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 21, 1930

The Influence of Carbon Dioxid Upon the Respiration of Unicellular Organisms.—WALTER S. ROOT (from the Department of Physiology, University of Pennsylvania, the Marine Biological Laboratory, Wood's Hole, Mass., and the Department of Physiology, Syracuse University). The respiratory exchange of *Paramecium caudatum* and the fertilized eggs of *Arbacia punctulata* have been studied by the methods of gas analysis.

At 15-mm. Hg. carbon dioxid tension the rate of oxygen consumption

¹ More recently, Dr. Henry Pinkerton, of the department of pathology, Harvard University (personal communication), has succeeded in demonstrating these minute intracellular organisms in the scrotal sac of guinea pigs infected with European typhus, even though the reaction be scarcely visible macroscopically.

of paramecia increases, reaching a maximum of 13 per cent above the control at 40 mm. At higher tensions the rate of oxygen consumption steadily decreases, crossing the control line at 66 mm. The average respiratory quotient in forty-eight controls was 0.623. The average value in forty-two carbon dioxid experiments was 0.961. The respiratory quotients increase as the tension of carbon dioxid increases, because the rate of carbon dioxid production remains relatively constant up to a carbon dioxid tension of 425 mm. Hg.

The rate of oxygen consumption and carbon dioxid production of fertilized arbacia eggs is decreased from the beginning in a linear relation to 30 per cent of the control at a carbon dioxid tension of 35 mm. Hg. At this point the curve bends sharply, falling as a straight line to 20 per cent of the control at 180 mm. Hg. The average respiratory quotient in thirty-two control experiments was 0.711. The average value in twenty-six carbon dioxid experiments was 0.676.

Carbon dioxid causes an initial increase in the motility of paramecia followed by a decrease (personal communication from Mr. Orren Chase). It is suggested that the initial rise in the rate of oxygen consumption observed in the presence of carbon dioxid is dependent upon this increased motility.

The Rôle of Copper in the Setting and Metamorphosis of the Oyster.—H. F. PRYTHERCH (assistant aquatic biologist, U. S. Bureau of Fisheries). The most important and critical period in the life history of the oyster is that during which the fully developed larva cements itself to some clean, firm surface such as old shells or stones and then undergoes a metamorphosis into a spat and adult oyster. The term setting is applied to this process of attachment, which is a biologic reaction of a most positive character. A study of the setting reaction under natural conditions showed that it occurred during the low-water stage of the tide or, in other words, when river discharge had its greatest effect on the physical and chemical condition of the water over the oyster beds. The environment of the oyster is the most complex, from a physical and chemical standpoint, of any on the globe, and at periods of low tide we find the extremes of many factors, as the mixing of fresh and salt water is taking place. Experiments with the oyster larvæ under controlled laboratory conditions showed that changes in temperature, salinity, hydrogen-ion concentration, oxygen content, CO₂ tension, and water pressure would not, in a single instance, induce the setting reaction. However, if in reducing the salinity, river water was used instead of distilled water, the larvæ gave a positive setting reaction which indicated that there was some substance in the river water which served to stimulate and control their attachment and metamorphosis. Further experiments involving variations in the amount and proportion of the cations and anions of the neutral salts were found to be ineffective in producing setting of the larvæ as were also the compounds of iron, zinc, tin, lead, aluminum and silver. The only element that produced a positive setting reaction was copper in the form of a pure metal or as a carbonate, sulphate, or chlorid. This heavy metal was effective in concentrations of one part copper to 5 million or 10 million parts of sea water and it initiated the setting process almost immediately. In the river water, copper was found to be present in relatively this same amount, and it is the specific element that is necessary for the attach-

ment, metamorphosis and survival of the oyster. River water from which the copper had been removed by precipitation and filtration was no longer effective in producing setting.

Cytologic studies of the larva showed that during its development there were gradually being deposited near the liver two dark green pigmented bodies which disappeared with its metamorphosis into the adult form. These pigment spots on closer examination were found to consist of a mass of densely packed leukocytes containing numerous green-colored granules. When the setting reaction begins the pigment spot breaks up rapidly, as approximately 300 leukocytes migrate from each into the blood stream, and by greatly increasing its oxygen-carrying capacity supply an effective mechanism for the rapid growth and development which follows. The rate of growth of the larva and its metamorphosis were found to be controlled largely by its ability to obtain this essential element in the form of free metal ions when the mixture of salt and fresh water is taking place.

Since copper plays such an important rôle in the respiratory processes of the oyster, it is to be expected that growth and development of the organism will be controlled to a large extent by the presence and availability of this important element in its environment.

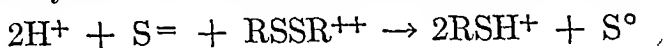
The Mechanism of Curarization.—W. A. H. RUSHTON (from the Johnson Foundation for Medical Physics, University of Pennsylvania). There are many conditions which abolish conduction from nerve to muscle, although neither individual tissue has lost its conductivity. This state is curarization in the broad sense of the word, and two mechanisms have been proposed to account for it. Claude Bernard postulated a susceptible intermediate substance whose conductivity was abolished earlier than that of muscle or nerve. Lapicque postulated that conduction was only possible between tissues of approximately the same chronaxie, and that curarization is due to the alteration of the time relations of one tissue relative to the other.

In a previous communication to this society evidence was given suggesting strongly that the nerve-muscle complex contains two excitable substances of very different chronaxies. The substance isochronous with nerve was identified with the intramuscular nerve twigs, whereas the chronaxie of the muscle substance itself was some twenty times as great. If this is true, Lapicque's theory of curarization would require that impulses could not pass from nerve to muscle even under normal circumstances.

The effects of curare and of fatigue through the nerve were the same and as follows: The substance identified with muscle suffered no change in threshold for any duration; that identified with nerve twigs was abolished at the same time as the failure of excitation through the nerve, and a typical muscle curve was revealed in its place. These results confirm the former identification of the two excitable substances in muscle, and confirm Claude Bernard by showing that curarization occurs when there is no excitability change at all of the muscle substance.

Lapicque's experiments upon the antagonism of strychnin and veratrin were repeated, but his results were not confirmed. Strychnin cause a rise in nerve threshold but no change in chronaxie, nor was it ever observed to restore indirect excitation which had been abolished by veratrin.

Mercury Derivatives of Cystein.—JAMES C. ANDREWS and PAULINE D. WYMAN (from the Department of Physiological Chemistry, University of Pennsylvania). The method of preparing cystein described by HARRIS (*Proc. Roy. Soc. (Lond.)*, Series B, 1913, 94, 441) has been shown by ANDREWS (*J. Biol. Chem.*, 1926, 69, 209) to result in only about 85 per cent reduction. The method consists in precipitating cystein with mercuric sulphate and treating the compound formed with hydrogen sulphid. Mercuric sulphid is precipitated and the greater part of the cystin is reduced to cystein. Since cystin alone in acid solution is not reduced by hydrogen sulphid, the reduction occurring when the mercuric sulphate compound is used has been attributed to some catalysis inducted by the simultaneous precipitation of the HgS and liberation of the free cystin. In such a case the reaction involved should be:



that is, free sulphur, equivalent to the cystin reduced should be precipitated along with the HgS. However, repeated attempts to identify free sulphur in the precipitate have always failed.

Our investigations of the composition and properties of this mercuric sulphate compound also brought out several facts which were not explainable on the assumption that the compound was one of cystin and mercuric sulphate. For example, analysis showed the compound to contain 3 atoms of mercury to 2 of nitrogen (corresponding to 3 mercury to 1 cystin) whereas potentiometric titration of cystin with mercuric sulphate solution gave a sharp minimum on the voltage curve at a ratio of 1 mercury to 1 cystin.

Similar investigations by VICKERY and LEAVENWORTH (*J. Biol. Chem.*, 1930, 86, 129) with silver salts, led them to conclude that when silver salts react with cystin the precipitate formed is silver cystein instead of silver cystin, and that the cystein is formed by a mutual oxidation-reduction reaction of the Canizzaro type whereby cysteic acid is the oxidation product. In testing this suggestion in the light of our results with mercury we find surprisingly good confirmation. If the precipitate obtained from mercuric sulphate on cystin already represents the reduced compound, no free sulphur should be formed. The 1 to 3 cystin to mercury ratio represents equally well a 2 to 3 cystein to mercury ratio with 1 mercury substituted for the 2 hydrogen atoms of the sulphydryl groups of 2 cystein molecules and the other 2 mercury atoms added to the two amino groups. This structure fully explains the potentiometric results: the introduction of the first mercury atom is accompanied by reduction of cystin to cystein, the other 2 mercury atoms are merely additive. Hence only the first would cause a break in the voltage curve.

Filtrates from the precipitation of 1 cystin with excess mercuric sulphate have always been dextro-rotatory. This supports the hypothesis of cysteic acid which has the value:

$$[\alpha]_b = +8.25$$

The hypothesis of a mutual oxidation-reduction whereby cystin is simultaneously oxidized to cysteic acid and reduced to cystein is of decided biologic interest in connection with the formation of taurin in the body.

Editor's Statement.

WE announce with regret that it has just been brought to our attention that in the article by Carlo J. Tripoli on "A Study of Stools Cultured for *Endameba Histolytica* for Diagnostic and Other Purposes" in the December, 1929, number of THE AMERICAN JOURNAL OF MEDICAL SCIENCES (vol. 178, p. 822) several extensive statements occur that had previously appeared in articles by Drs. Clifford Dobell and P. P. Laidlaw (in *Parasitology*, 1926, 18, 283), and by Dr. J. H. St. John (*Am. J. Trop. Med.*, 1926, 6, 319), copied either *verbatim* or with the change of a few words in the course of several sentences. These repetitions were not enclosed in quotation marks, nor was their source acknowledged in any way, except that the original authors' names and articles were included in the list of references. Communication with Doctor Tripoli and those under whom the work was done indicates that the work was primarily prepared as a class exercise and that the author—a medical student at the time—wrongly considered it legitimate to make even lengthy excerpts from the articles of others if reference to the articles was made in the bibliography. The minor textual changes were made by those to whom the manuscript was shown, who, like the editors, were unaware that the material had been copied.

We wish to express to Drs. Clifford Dobell and P. P. Laidlaw, and to Dr. J. H. St. John our deep regret that parts of their articles should have thus appeared in our JOURNAL without the customary proper acknowledgment.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

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Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.

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